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TABLE OF CONTENTS FIRST PAGE

A SCIENTIFIC CORNER

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THE SOLUTIONS, AS SOLVED BY EXPERIENCE, INDICATED!

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We have the case of Mr. D who was unable to use his bifocals at his desk. His correction was R.E. —0.25 sph. L.E. —0.25 —0.25 cx 110, add to both: + 1.75. The bifocal line annoyed him and the scope through the segments was not large enough to take in all of his desk without constantly adjusting his head position.

Mr. D. then tried straight reading glasses which, while they solved his near problem, were so blurred for distance that he could not wear them.

The patient was fitted with Ultex "AA" bifocals with the segments set 24 mm. high. The segments were large enough to take in his entire desk and there was enough distance portion for him to see around the office when he looked up from his work.

Care was taken to make sure the patient understood that the glasses were for desk use only. Unless that fact is well in mind, patients are often disgruntled because they cannot wear their occupational bifocals on the street.

The three most widely used occupational bifocals are the Ultex "AA", the Ultex "L" and the Rede-rite. Below are sketches of these bifocals with notes on the segment sizes.

Figure 1 shows the Ultex "AA" bifocal which has a segment 38 mm. in diameter. The segment may be placed as high as 32 mm.

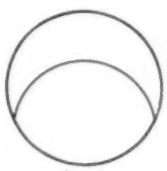

Fig. 1

The Ultex "L" is shown in figure 2. The Ultex "L" has a segment 32 mm. in diameter: 28 mm. is the maximum seg height.

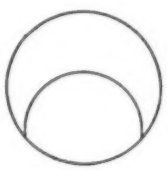

Fig. 2

Figure 3 shows the Rede-rite bifocal, which is really a reading lens with a small distance window. The bottom of the upper segment cannot be placed more than 19 mm. from the top of the lens.

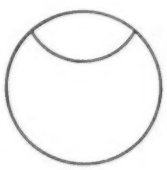

Fig. 3

"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

CONTENTS

Original Articles

PAGE

Juxtapapillary Malignant Melanoma of the Choroid and So-Called Malignant Melanoma of the Optic Disc

J. Arnold deVeer, M.D., Brooklyn 147

Notching of the Optic Chiasm by Overlying Arteries in Pituitary Tumors

C. Wilbur Rucker, M.D., and James W. Kernohan, M.D., Rochester, Minn. 161

Radioactive Phosphorus as a Diagnostic Aid in Ophthalmology

J. W. Bettman, M.D., and Victor Fellows, M.D., San Francisco 171

Dacryocystography

Benjamin Milder, M.D., and Byron H. Demorest, M.D., St. Louis 180

Bacteriology of the Eye

I. Normal Flora

Louise Cason, M.A., and C. H. Winkler Jr., Ph.D., Birmingham, Ala. 196

II. Role of Gram-Negative Bacilli in Infections Following Cataract Extraction

C. H. Winkler Jr., Ph.D., and Louise Cason, M.A., Birmingham, Ala. 200

Ocular Signs of Wernicke's Disease

David G. Cogan, M.D., and Maurice Victor, M.D., Boston 204

Contact Lenses in Aphakia

Elizabeth F. Constantine, M.D., and John M. McLean, M.D., New York 212

The H-R-R Polychromatic Plates

LeGrand H. Hardy, M.D.; Gertrude Rand, Ph.D., and M. Catherine Kittler, B.A., New York 216

Ocular Manifestations of Infectious Mononucleosis

O. R. Tanner, M.D., Palo Alto, Calif. 229

Studies in Experimental Ocular Tuberculosis

Alan C. Woods, M.D.; Bernard Becker, M.D., and Ronald M. Wood, Ph.D., Baltimore 242

Annual Reviews

Cornea and Sclera

Trygve Gundersen, M.D., Boston 256

Correspondence

Diabetic Retinopathy

Louis Pelner, M.D., and Samuel Waldman, M.D., Brooklyn 282

Regular Departments

News and Comment 285

Books 286

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4. Wolman, B., et al.: Brit. M. J. *1*:419 (Feb. 23) 1952.
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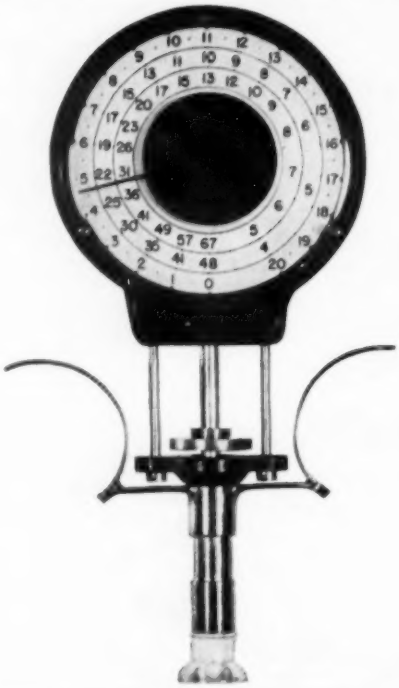

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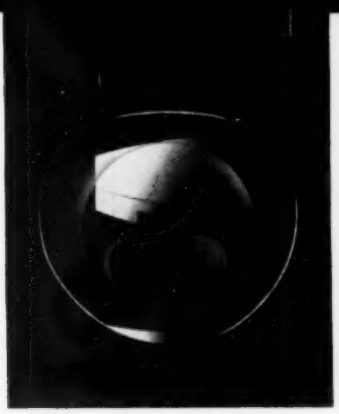

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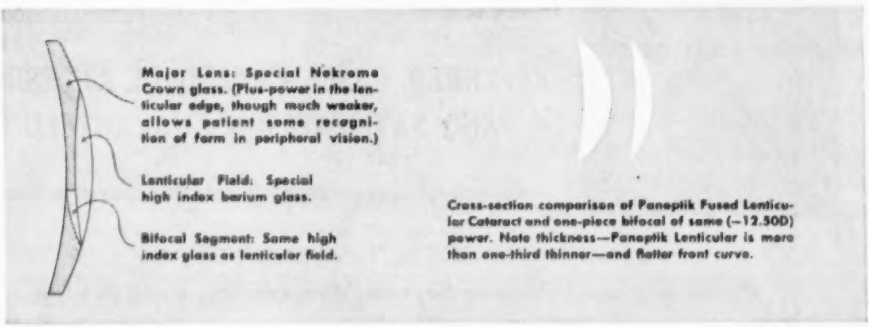
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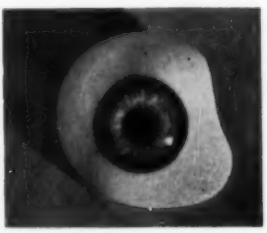

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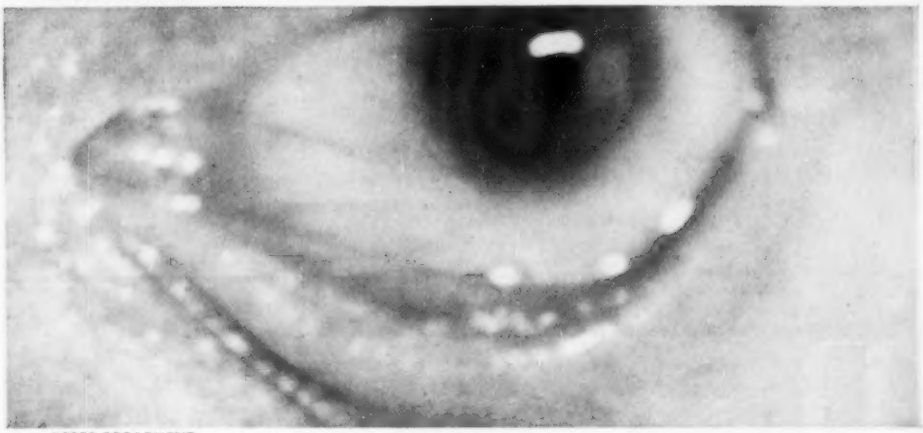

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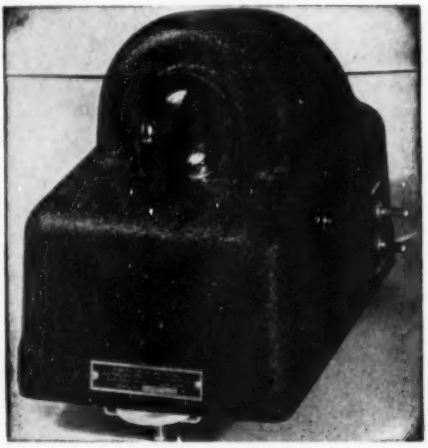

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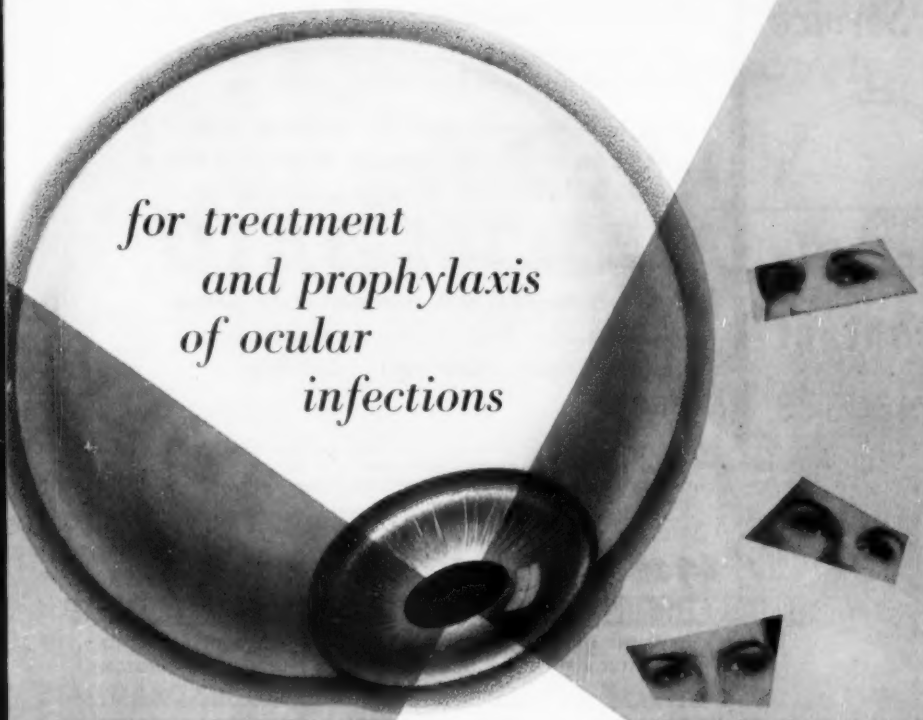

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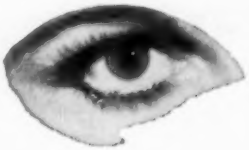

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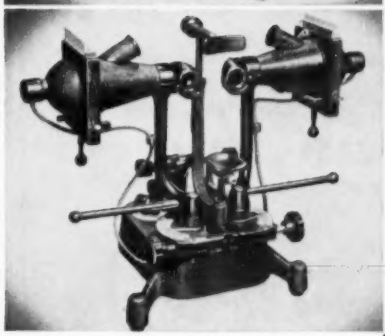

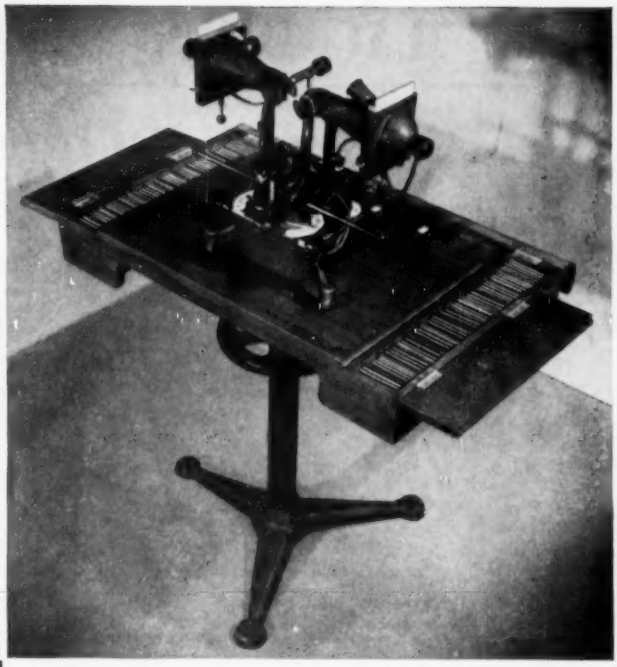

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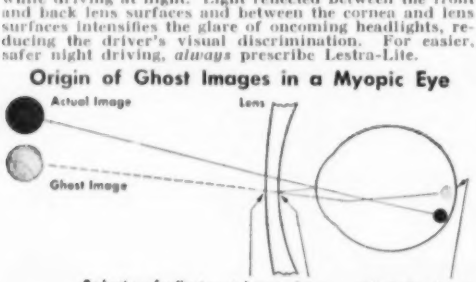

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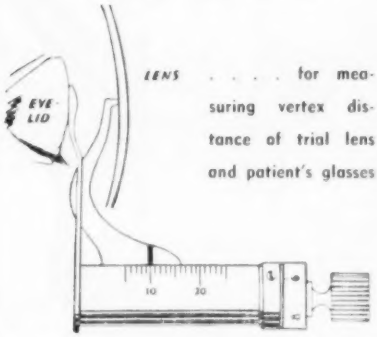

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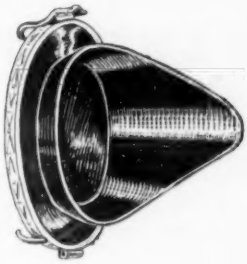

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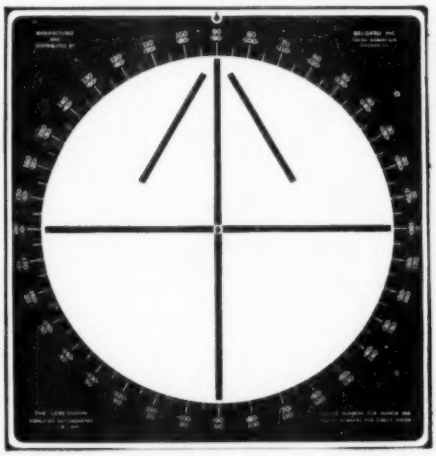

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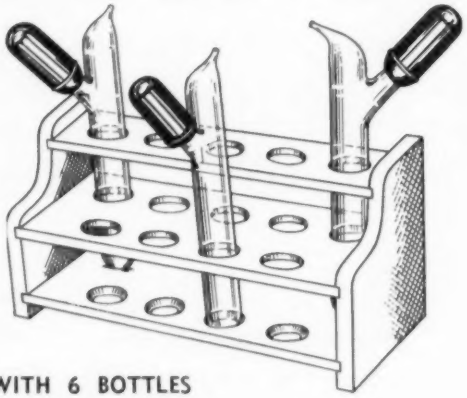

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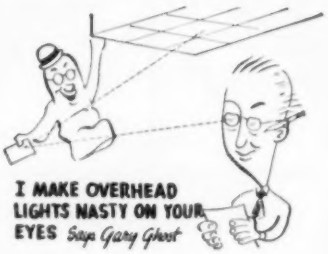

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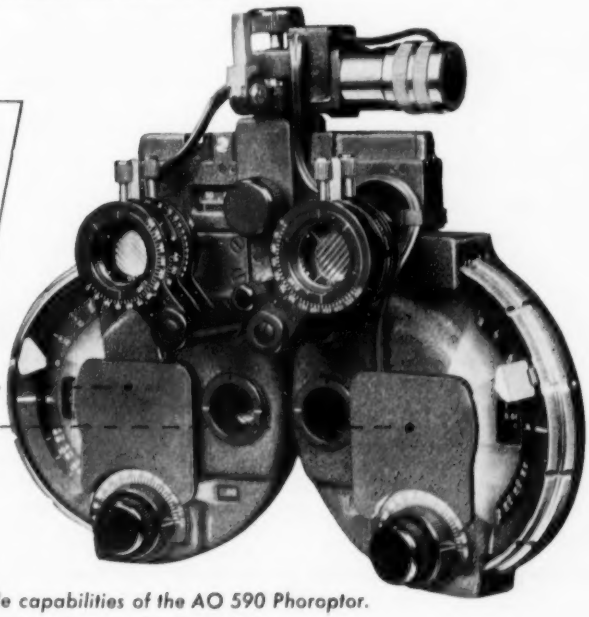

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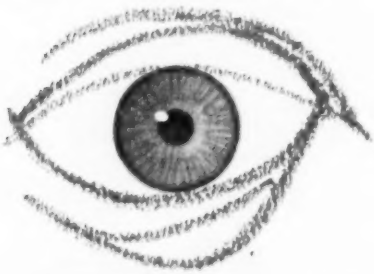

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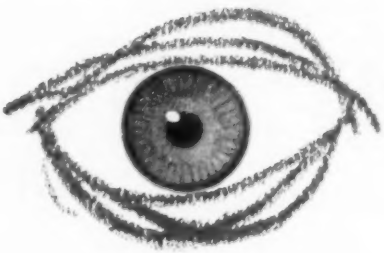

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2. Stolzar, I. H.: Am. J. Ophth. 36:110 (Jan.) 1953.

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JUXTAPAPILLARY MALIGNANT MELANOMA OF THE CHOROID AND SO-CALLED MALIGNANT MELANOMA OF THE OPTIC DISC

A Pathologic Study

J. ARNOLD deVEER, M.D.
BROOKLYN

MALIGNANT melanomas occasionally manifest themselves clinically as more or less pigmented growths within the substance of the optic nerve head. In most instances such lesions are found, on histologic examination, to be situated in part within the choroid adjacent to the nerve structures as they course backward from the nerve fiber layer of the retina to become the optic nerve. These lesions have been called juxtapapillary malignant melanomas of the choroid. In some instances, it has been difficult to decide just where the tumor originated, and, very rarely, it has been contended that the growth arose from structures within the nerve head.

The first purpose of this report is to present an example of a pigmented tumor involving the nerve head but rather obviously having taken origin from an adjacent site in the choroid. The portion of the tumor within the nerve substance was identical in gross appearance and histologic structure with certain tumors that have been considered primary growths of the optic disc.

REPORT OF A CASE

Clinical Data.—M. S., a 48-year-old man, was seen on April 29, 1952, by Dr. Mortimer A. Lasky, who furnished the following clinical data. The patient complained of recent loss of vision in the left eye. Cystoid degeneration of the macula and pigmentation of the nerve head and of the retina superior and inferior to the nerve head were noted. After a period of observation of seven months, during which the disc became solidly pigmented, the eye was enucleated.

Pathologic Examination.—The enucleated eye was of approximately normal size and shape. Calottes having been cut parallel with the horizontal meridian, the optic nerve head was seen to be slightly elevated. Its coats were rather thin, and the retina remained almost completely attached during the process of fixation and embedding, suggesting possible glaucomatous atrophy. There was slight thickening of the choroid along the posterior margins of the calottes, and these sites were shown by sectioning in paraffin to contain malignant melanotic tumor. The remainder of the bulb was embedded and sectioned in pyroxylin. The choroidal tumor was of the "flat" type, extending from just to the nasal side of the optic nerve head to beyond the macula, covering an area approximately circular and 1.5 cm. in average diameter. The mass averaged 1 mm. in thickness. It was moderately but irregularly pigmented. The tumor had extended to the supervaginal space about the optic nerve (Fig. 1).

Of particular interest was the condition of the optic nerve head. Here, there was somewhat heavier pigmentation than elsewhere as the result of an infiltration that extended from the lamina cribrosa forward in a fan-like pattern toward the surface of the papilla and adjacent retina. Toward the inner surface of the pigmented area the dark coloration was chiefly perivas-

From the Departments of Pathology of the Brooklyn Hospital and the Brooklyn Eye and Ear Hospital.

cular. Small blood vessels were evidently more numerous than is normal, but perhaps only more conspicuous because of their melanotic mantles (Fig. 2). Details of histologic structure were more or less obscured by melanin, but masses of cellular tumor of predominantly spindle type were present in both the choroid and the nerve head and could be seen curving around the margin of the lamina vitrea to enter the enlarged papilla (Fig. 3). In addition, the pigmentation

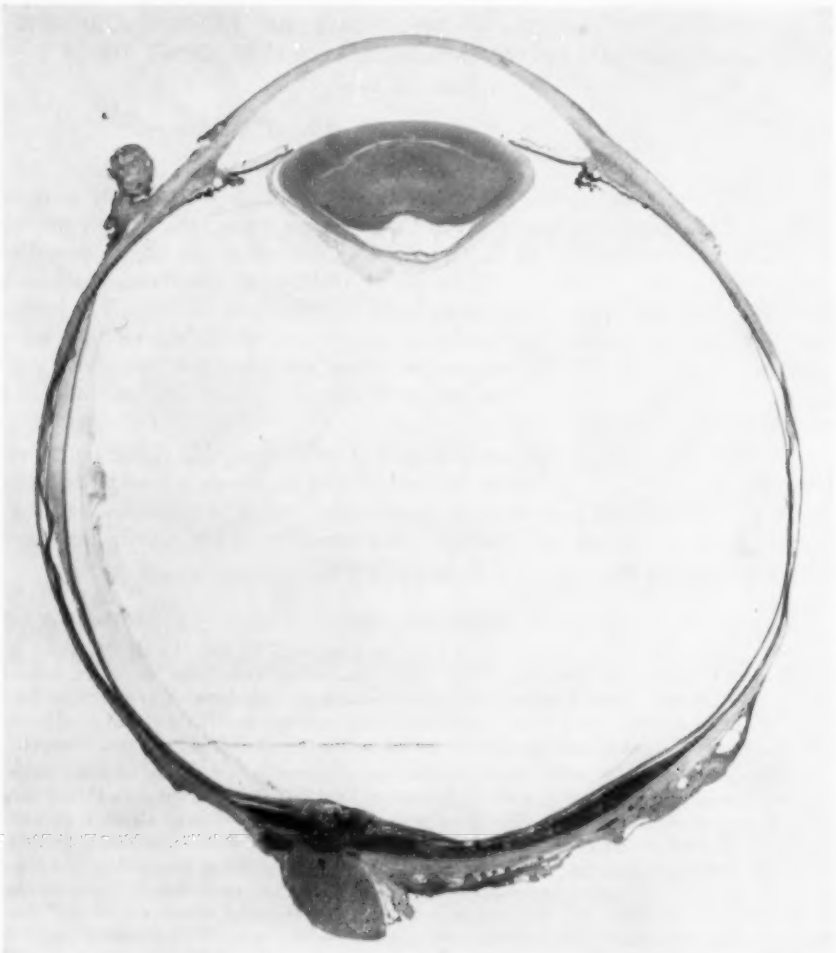

Fig. 1.—The entire bulb, showing a "flat" tumor in the choroid and optic nerve head.

of the nerve tissue was seen to be partly within elongated branching cells of the appearance of chromatophores. Cells of the latter type seemed almost exclusively to constitute the mantles about the blood vessels (Fig. 4).

Bleaching out most of the pigment revealed tumor of mixed (spindle B and fascicular) type both in the choroid and in the deeper portion of the papilla (Fig. 5). The loss of pigmentation surprisingly altered the appearance of the branching cells, so that in many areas they no longer looked neoplastic. This was especially noted at the margins of the papilla and in the adjacent

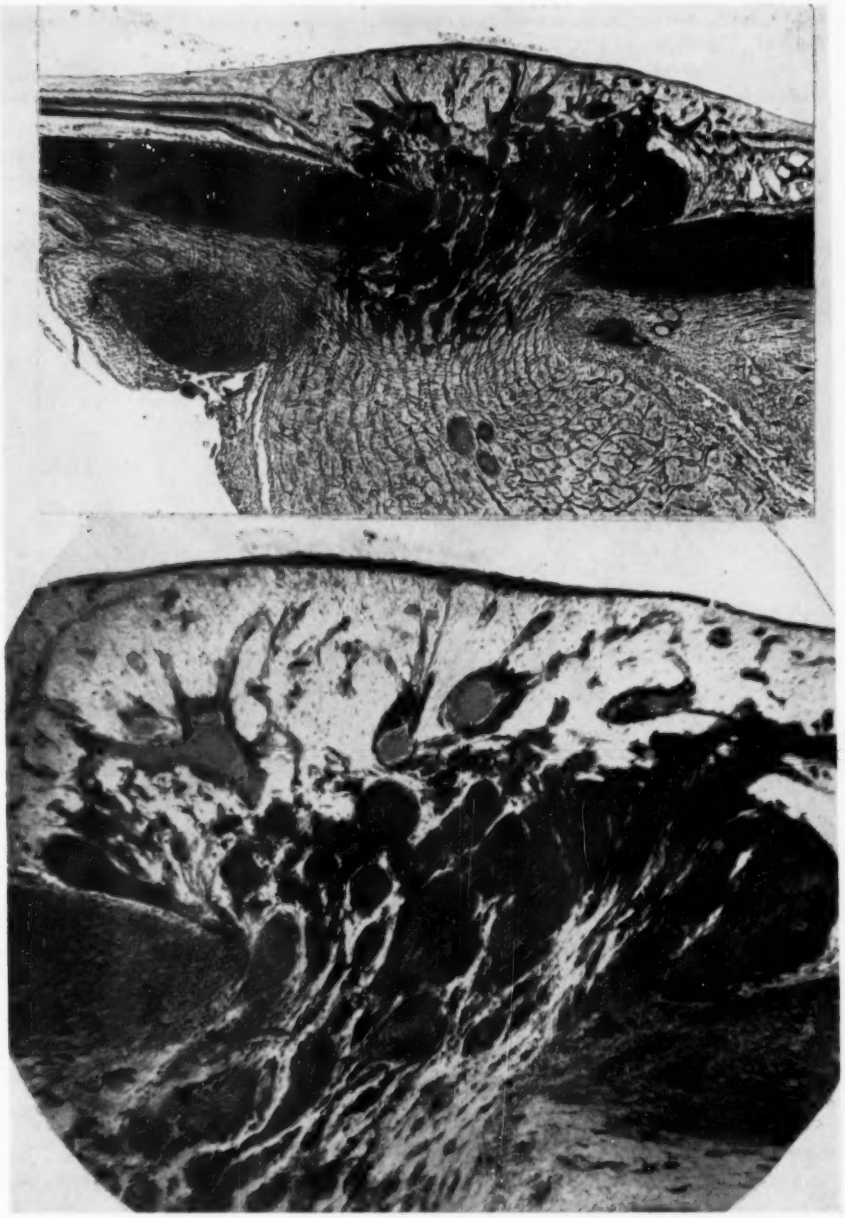

Fig. 2.—Tumor tissue in the choroid encircles the nerve entrance. From the lamina cribrosa forward there is pigmentation that fans out into the papilla. In the more superficial portions the pigmented structures are chiefly perivascular. Neoplastic tissue can also be seen in the supervaginal space to the left of the nerve and in a smaller focus to the right of the nerve.

nerve fiber layer of the retina where, it was concluded, the pigmentation must have been chiefly contributed by non-neoplastic macrophages of chromatophore morphology * that carried ingested pigment (Fig. 6).

Of collateral interest was the presence of fibrosis within the tumor-bearing portion of the choroid behind the macula, where there was so-called disciform degeneration (Fig. 7). The remainder of the bulb was not significantly abnormal.

The lesion was considered a malignant melanoma of the choroid with secondary involvement of the papilla. A comparison of this type of tumor of the papilla with reported cases in which the growth was believed to be primary in the optic nerve head was undertaken.

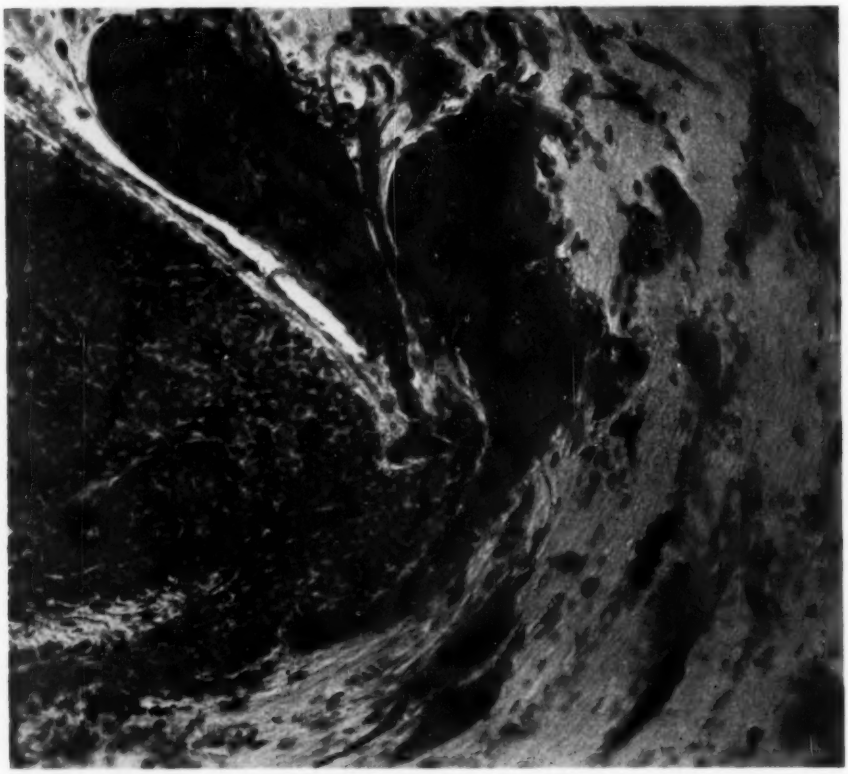

Fig. 3.—The tumor-filled choroid to the left is continuous with tumor that has grown around the margin of the lamina vitrea into the substance of the papilla

REVIEW OF CASES REPORTED AS MALIGNANT MELANOTIC TUMORS OF THE PAPILLA

The reported cases of malignant melanoma apparently primary in the nerve head were reviewed, proceeding from the following premises:

1. The contention that malignant melanomas may arise as primary neoplasms of the optic disc has, perhaps, been based on inconclusive evidence. Reviewers of

* The source of the non-neoplastic pigment-containing cells in this situation is probably the monocyte, which has been shown to undergo transformation in tissue culture into microphages, epithelioid cells, and multinucleated giant cells.

the subject have not always been sufficiently critical, and there is, in my opinion, room for doubt of the occurrence of such a lesion.

2. If some, but not all, of the reported cases seem to be authentic examples of melanotic neoplasms originating in the optic disc, the concept of the primary nature of that lesion would be better supported by a small valid group of cases than by a larger group some of which are obviously or possibly not authentic.

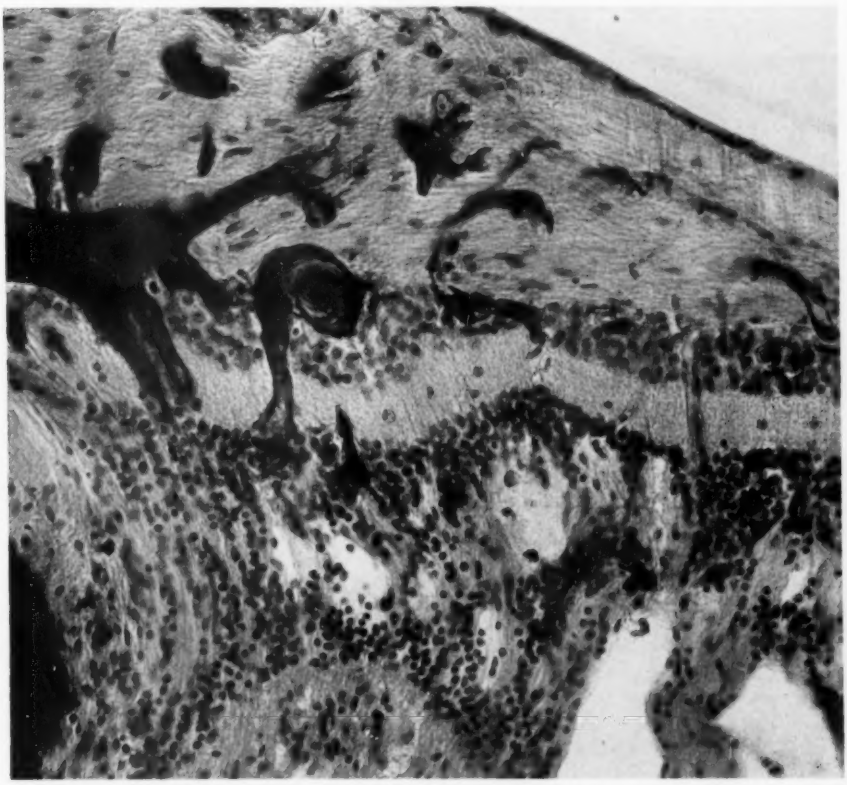

Fig. 4.—The more peripheral parts of the papilla and adjacent retina show the pigmentation chiefly about blood vessels.

3. Pathologic "entities" that are exceedingly uncommon may actually be unusual examples of commoner lesions.

4. To establish as a fact the occurrence of an "entity" so rare as to be almost nonexistent requires presentation of proof that will withstand the most rigorous analysis.

The subject of primary malignant melanoma of the disc is considered to some extent in three recently published textbooks dealing with ophthalmic pathology. Samuels and Fuchs [1] make the statement that "apparently a melanosarcoma of the

papilla or optic nerve hardly ever originates as a primary tumor." In the publication "Ophthalmic Pathology" [2] (sponsored by the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology) it is stated that "a number of melanotic tumors of the nerve head have been reported and are regarded as of melanoblastic origin, since branching pigmented cells are sometimes seen in the normal lamina cribrosa, particularly of Negroes in whom these tumors are more common." The case reported by Cordes and Hogan is referred to as follows, "serial sectioning demonstrated absence of choroidal involvement."

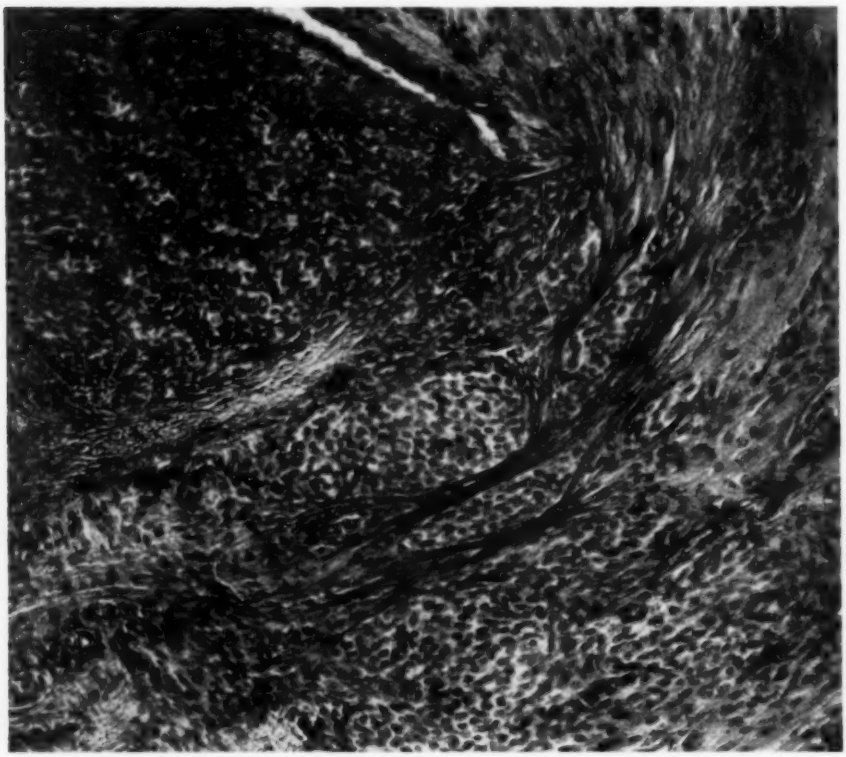

Fig. 5.—Depigmentation revealed a mixed (spindle B and fascicular) type of tumor in the region of the margin of the disc.

In Reese's [3] monograph, eight cases are listed as having been "verified microscopically" as examples of primary malignant melanomas of the papilla which arose in the region of the lamina cribrosa. The cited cases were those reported by Vazquez-Barrière,[4] Murray,[5] Oloff,[6] Speciale-Cirincione,[7] Oguchi,[8] Levine,[9] Cordes and Hogan,[10] and Fry and DeLong.[11]

In presenting their case, Cordes and Hogan, in 1941, reviewed the literature and, after discussing cases previously reported, accepted only five as having been satisfactorily proved. Their list includes a report by Cosmettatos.[12]

Duke-Elder [13] states, "Simple melanomata forming pigmentary plaques occur not infrequently on the optic disc presumably arising from uveal elements incorporated in its tissues. Malignant melanomata, however, are a rarity." He cites six cases, all of which, with the exception of that of Bucalossi,[14] have been mentioned above.

It must be pointed out that several of the 10 cases listed above cannot possibly be allowed to stand as proved examples of this supposed entity. Even at the risk

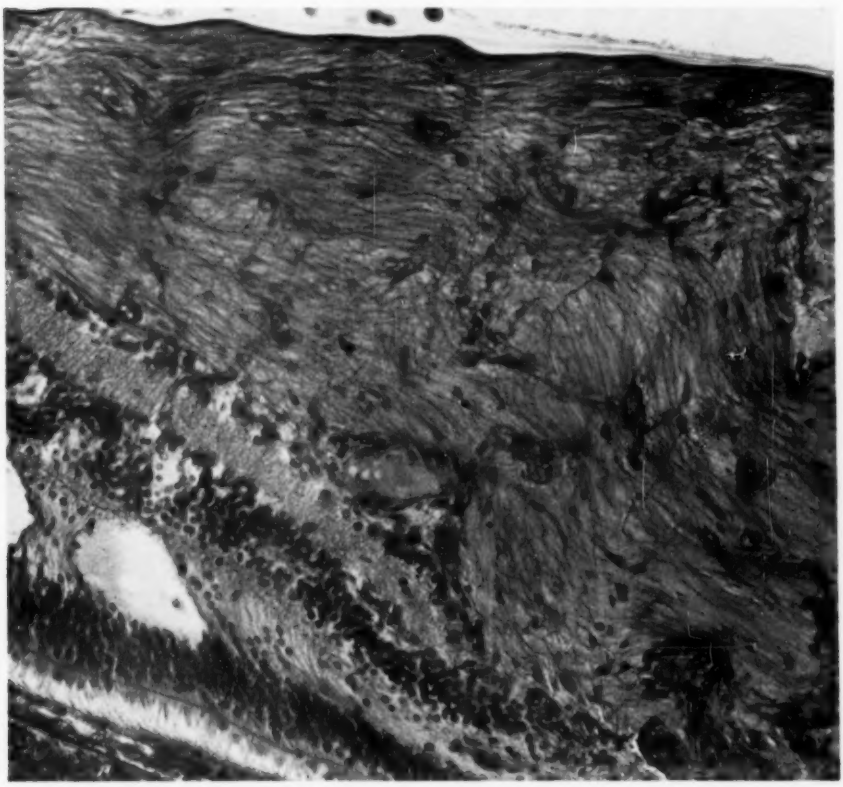

Fig. 6.—When deprived of most of its pigment, the involvement of the inner parts of the disc and of the adjacent nerve fiber layer of the retina lost most of its neoplastic appearance. Pigmentation in this region was evidently produced by pigment-bearing macrophages (chromatophores).

of appearing to be hypercritical, a reconsideration of each case would therefore seem to be justified.

1. Murray's case was reported in 1911 as an instance of "sarcoma of the optic disc." Histologic examination was made by Dr. J. M. Wainwright, who reported that "the tumor lies between the sclera and the retina. The portion of the retina lying stretched over the tumor is considerably thinned out and disorganized so that its characteristic anatomical structure is lost. The tumor itself has no definite

capsule, but is sharply limited by the sclera. The tumor cells do not invade the sclera at all. There is considerable diffuse infiltration of tumor cells in the loose connective tissue, lying in the angle between the retina and sclera at the point where they separate to cover the tumor." His own drawings of the lesion plus the vague description leave no doubt that Wainwright found tumor tissue within the choroid. His report does not even mention the optic disc. This case must surely be excluded. Cordes and Hogan also considered it unacceptable.

2. Vazquez-Barrière's case (1911) was one in which there was tumor in the choroid, as well as in the optic nerve. Axenfeld, the teacher of Vazquez-Barrière,

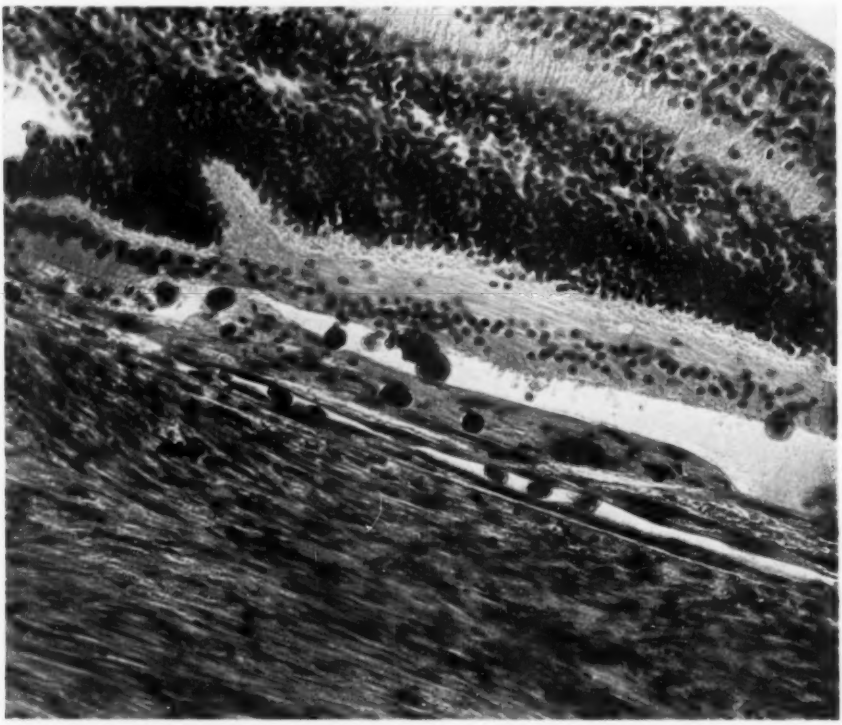

Fig. 7.—Behind the macula, which was cystic, the tumor in the choroid was intermingled with fibrosis. A layer of adventitious tissue was interposed between the lamina vitrea and the retina. This tissue had evidently been produced chiefly by proliferation of the cells of the pigmented epithelial layer.

concurred in the interpretation of this case as one of malignant melanoma of the papilla. Fry and DeLong thought that the tumor probably originated in the choroid. In my opinion, this case, although suggestive of possible origin in the papilla, cannot furnish the conclusive evidence necessary to establish the fact of the occurrence of a previously unknown entity.

3. Oloff's case (1915) was one in which clinical and gross anatomic examinations only were made. Some of the tissue was lost during Germany's mobilization for the war. The author promised to publish a microscopic report after the war in

the event that the material should be recovered. I have been unable to find any record of a subsequent report. This case, then, must be excluded as lacking verification, a conclusion also reached by Cordes and Hogan.

4. Cosmettato's case (1923) was one in which exophthalmos had been produced by two tumors, one behind the other along the course of the optic nerve and measuring 3 and 2.5 cm. in diameter. The nerve on macroscopic examination could be seen passing through the center of one of the tumor nodules but was found microscopically to be infiltrated by tumor cells in both nodules. The eye itself was not

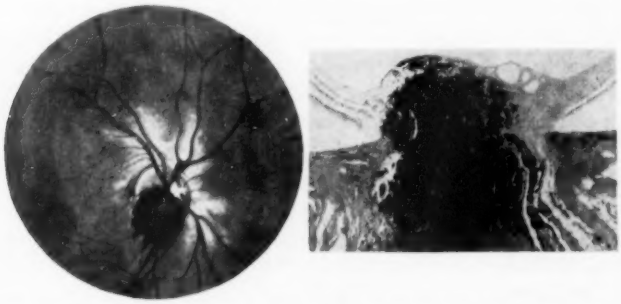

Fig. 8.—Illustrations from the paper by Cordes and Hogan [10] (reproduced from *American Journal of Ophthalomology*). This lesion was considered a primary malignant melanoma of the papilla.

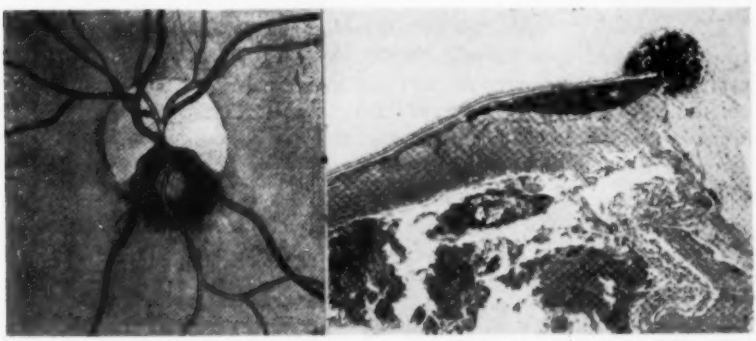

Fig. 9.—Rönne's [20] illustrations of a juxtapapillary choroidal tumor invading the nerve head (reproduced from *Transactions of the Ophthalmological Society of the United Kingdom*). Note the similarity of the fundal drawing to that in Figure 8. Sectioning in the vertical midline showed tumor that had grown from the choroid into the lower half of the disc only.

invaded by tumor but was shriveled. The growth was considered by the author to be a round-cell sarcoma of the optic nerve originating in the connective tissue that accompanies the central vessels into the nerve. There was no mention of the papilla except that ophthalmoscopic examination showed *une forte stase papillaire* (marked papillary congestion) with hemorrhage along the retinal vessels. I could find no reference to pigmentation. It was stated, "the protoplasm is clear." Cordes and Hogan include this case among the five that can be considered "proved," stating that the tumor involved the intraocular portion of the optic nerve, as well as the

nerve behind the lamina cribrosa, and that there was no choroidal involvement. They cite Reese's [15] previously reported opinion in support of their view. The case, however, is not included in that author's later list of eight verified cases. I cannot escape the conclusion that the tumor was a huge, bilobular meningioma, not remotely suggestive of the lesion under consideration.

5. Speciale-Cirincione, in 1925, reported a case of "sarcoma of the optic disc." Tumor in the choroid had encircled the disc and displaced and infiltrated the tissue of the papilla. Fry and DeLong believed this to be a case of tumor primary in the choroid. Duke-Elder [16] refers to this report in a discussion of juxtapapillary malignant melanoma, but gives the same reference in listing reported cases of malignant melanoma of the optic disc.[12] Cordes and Hogan, and Reese included it among their cases of melanotic tumors of the papilla. In my opinion the case belongs in the category of juxtapapillary malignant melanomas of the choroid with secondary involvement of the nerve head; origin in the disc was certainly not proved.

6. Oguchi's case (1933) was one of the few in which the tumor was confined almost entirely to the nerve head. Only one point of criticism seems justified, namely, that the direction of sectioning of the bulb was horizontal—across the shorter diameter of the mass in the nerve head—whereas the tumor was elongated in the vertical meridian, where it measured "two and a half to three disc diameters." Illustrations are from levels where the tumor is within the papilla and little wider than the papilla. They do not explain what was happening at the superior and inferior limits of the lesion. It must be concluded that this case is at least highly suggestive of a primary neoplasm of the optic disc, but vertical sectioning might have furnished more conclusive evidence or might have shown choroidal involvement.

7. Levine, in 1935, reported a case in which the tumor was almost strictly confined to the disc and optic nerve in the region of the lamina cribrosa. The patient, however, had had a pigmented mole "about a ¼ in. in diameter" excised from the skin of the leg, because of persistent itching, somewhat more than a year before discovery of the ocular tumor. Six months after enucleation, at the time of reporting, the patient stated that his health was excellent.

A personal communication from the author in April, 1953, gave the surprising information that the man was still alive and was well. My suspicion that the ocular lesion had been a metastatic tumor primary in the skin is not strengthened by this long survival (19 years). The author wrote that he had recently reviewed the sections and found evidence of malignancy in the ocular tumor.

It is well known that the intervals between the dates of enucleation and of appearance of metastases have rather frequently been from 10 to 18 years, and in one instance, William H. Wilder's case,[17] 32 years had intervened.†

There may also be a long latent period between the time of excision of a "mole" of the skin and the appearance of metastases (Willis [18]). Instances in which metastatic tumors, some of them solitary, had developed as long as 10 years after excision of a "mole" are cited by Willis.[19] Cordes and Hogan, in discussion of the

† Only the following mention of this case is made in a report of a meeting of the Chicago Ophthalmological and Otological Society of Oct. 9, 1900. "Some years ago in the laboratory of Professor Kundrath, in Vienna, William H. Wilder saw a specimen of melanotic sarcoma of the liver in a subject who, 32 years before, had had one eye enucleated for sarcoma of the choroid."

problem in Levine's case, referred to four instances in which metastases appeared in the eye one year after removal of a growing congenital pigmented nevus. The long survival in Levine's case is also of interest in view of the statement in "Ophthalmic Pathology," [2] in discussion of melanotic tumors of the nerve head, that "although these tumors may be locally invasive and histologically appear malignant, there is no recorded instance of metastasis."

Disregarding the remote possibility that Levine's tumor was a metastatic lesion, there would seem to be a justifiable doubt concerning origin in the papilla rather than at the disc margin in the choroid. The tumor had produced a bluish discoloration and protrusion of the upper temporal portion of the disc. Sections shown are all from the horizontal midline, and these show no choroidal involvement. The evidence is highly suggestive, but hardly of the conclusive nature required to prove the origin of an entity of questionable source.

8. Bucalossi's case, reported in 1935 as one of a lightly pigmented polymorphic-celled sarcoma of the papilla, was one in which there was rather extensive choroidal involvement. Cordes and Hogan refer to this case as one in which the tumor had its origin in the choroid.

9. Fry and DeLong, in 1942, reported a case in which a pigmented mass was found at the margin of the optic disc. The authors reported the lesion as a malignant melanoma probably originating in choroidal elements at the lower inner border of the disc. Verhoeff, who studied the sections, agreed that it was not a tumor of the papilla but further stated in discussion of this case, "It is not a melanoma." From further recorded discussion, as well as from the authors' description and illustrations, the impression is gained that there was uncertainty both as to the nature and as to the site of origin of the tumor. There seems, therefore, little justification in including this case among instances of verified primary melanotic tumors of the papilla.

10. The case of Cordes and Hogan, reported in 1949, is among the few impressive reports. Prior to consideration of this last in our list of 10 cases we might do well to take inventory of those already discussed.

One case (Oloff): No microscopic verification.

One case (Murray): Inadequate description—choroid involved.

Two cases (Cosmettatos, and Fry and DeLong): Probably not malignant melanomas—probably not primary in papilla.

Three cases (Vasquez-Barrière, Speciale-Cirincione, and Bucalossi): Choroid involved. Origin in papilla possible but not provable. Juxtapapillary origin more likely.

One case (Levine): Metastasis from skin of leg a remote possibility. If primary in the eye, juxtapapillary origin not conclusively excluded.

One case (Oguchi): Sections of papilla across the short diameter of an elongated tumor. Juxtapapillary origin not conclusively excluded.

Of these nine cases, only those of Oguchi and Levine remain free of causes for rejection, or at least grave impediments to acceptance as proved examples of primary malignant melanomas of the papilla; and even in those cases, in my opinion, it was not shown beyond doubt that the tumors could not have arisen in the uvea at the disc margin. We are forced to take up the case of Cordes and Hogan, not as the 6th or 10th (or thereabouts) of a series of examples of a rare entity, but as possibly the first proved case of a condition that had not been conclusively shown to occur during more than 50 years of clinical and histologic investigation. Under

such circumstances a considerable degree of skepticism seems justifiable; strong evidence would be required to prove the occurrence of this previously unproved "disease entity."

The pigmented tumor in Cordes and Hogan's case is pictured in a painting of the fundus with its center at the inferior disc margin. Its upper border reaches barely beyond the center of the disc. Calottes were said to have been cut vertically, as would be required to show in one plane not only the involvement of the disc but the portion of the mass inferior to the disc. On the other hand, the many excellent photomicrographs, selected from serial sections, all seem undoubtedly to be horizontal sections. None shows an uninvolved (superior) portion of the papilla; none shows the involvement of adjacent (inferior) retina, and all pass through the nerve entrance. It would appear to be a prime requisite that illustrations include the most peripheral portions of eccentric tumors presented as having originated in the substance of the optic nerve head. It is impossible to escape the thought that this tumor may have arisen in the choroid near the margin of the disc, and swept about the border of the lamina vitrea, as Rönne [20] and Reese [15] have so well demonstrated in other cases (Fig. 9), to invade the adjacent inferior portion of the papilla and subjacent retina. This case must therefore be considered as not proved beyond reasonable doubt.

CELLULAR CHARACTERISTICS OF SO-CALLED PRIMARY MALIGNANT MELANOMAS OF THE PAPILLA

The histogenesis of melanotic tumors in general cannot yet be said to be entirely understood. Those originating in the eye are no exceptions in this respect. No useful purpose would be served by reviewing this much discussed subject. It should be mentioned that some authorities believe that some of the malignant melanomas of the uvea arise in uveal melanoblasts, and this concept of derivation has been indicated by the use of such terms as "melanophoroma" (Friedenwald [21]), "stromal melanoma" (Reese [8]), etc. Schwann cells, the commoner source of uveal malignant melanomas, are not present in the papilla, but there are frequently some pigmented cells in the lamina cribrosa (a choroidal component of that structure). It is from these "stromal melanoblasts" that primary melanotic tumors of the nerve head are believed to rise. Proof of the occurrence of such tumors would lend support to the concept of the possible origin of melanotic tumors from stromal cells, and would therefore be of considerable academic interest.

I have not been impressed with any distinctive histologic structure that would label a pigmented tumor as being of "stromal" origin. The presence of large branching pigmented cells is a common feature of many tumors of "mixed" cellular composition. The following commentary quoted from "Ophthalmic Pathology" [22] is of interest in this connection.

> In the series of cases reported by Wilder and Paul [23] the branching cell was invariably associated with epithelioid and spindle cells and sometimes with fascicular arrangement. These tumors of mixed cell type are highly malignant. The much rarer tumors consisting only of melanophors are relatively benign as is to be expected from their highly differentiated cell form.‡

‡ The implied paradox of the occurrence of tumors that are relatively benign when composed purely of melanophores, and of other tumors that are highly malignant when composed of these same highly differentiated cells in admixture with cells of other types, some of which are not themselves highly malignant, is not explained.

Of the types enumerated the mixed is by far the most common, accounting for more than half of all malignant melanomas of ciliary body and choroid. Since each of these cell types can exist in combination with any of the others, it is most unlikely that they are cells of different cytogenesis. The strongest probability is that the distinctive characteristics of each of the cell types result from different modes of growth of tumor cells of the same origin.

In my opinion many of the "large branching cells" are macrophages that have phagocytized pigment, and not neoplastic cells. Judging from the various authors' descriptions, drawings, and photomicrographs, the cases referred to above are not of a histologic type distinct from those commonly encountered in the choroid.

SUMMARY AND CONCLUSIONS

It is well known that malignant melanomas arising in the choroid close to the optic nerve entrance may invade the optic nerve head and masquerade as primary tumors of the papilla.

A pathologic study of a juxtapapillary tumor of this type is presented. The portion of the tumor within the nerve head resembled that seen in other cases, some of which have been considered primary growths.

A prominent feature was the presence of a large amount of pigment within macrophages. Bleaching revealed that not all of the pigmented mass in the papilla was neoplastic.

Rarely, malignant melanomas have been reported as having originated in the papilla; such examples have not been uniformly interpreted by reviewers, and certain cases, accepted as proved by some authorities, have been rejected by others. The reports of 10 cases of so-called primary melanotic tumors of the papilla have therefore been critically evaluated. Undoubtedly these cases do not represent all published instances of tumors considered by the reporters or others to be examples of this condition, and no extensive search for such cases was undertaken. The 10 cases were selected as being representative and probably fairly inclusive. All were referred to in recent authoritative publications.

In my opinion no case in the group reviewed has conclusively been shown to be an example of malignant melanoma primary in the optic nerve head. In most of the few instances in which a malignant melanoma showed a major localization in the optic papilla the growth was eccentric and involved tissue beyond the margin of the disc. Origin at the margin, in choroidal tissue, seems to me to be a logical probability. Lack of convincing evidence of origin of a malignant melanoma in the papilla after more than 50 years of investigation suggests that perhaps no such lesion occurs.

REFERENCES

1. Samuels, B., and Fuchs, A.: Clinical Pathology of the Eye: A Practical Treatise of Histopathology, New York, Paul B. Hoeber, Inc., 1952, p. 382.

2. Ophthalmic Pathology: An Atlas and Textbook, sponsored by American Academy Ophthalmology and Otolaryngology, and the Armed Forces Institute of Pathology, Philadelphia, W. B. Saunders Company, 1952, p. 400.

3. Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951.

4. Vazquez-Barrière, A.: Bemerkenswerter Fall von Melanosarkom der Papille, Klin. Monatsbl. Augenh. **49**:43, 1911.

5. Murray, G. D.: Sarcoma of the Optic Disk, Ophthalmology **7**:11, 1910.

6. Oloff, R.: Über primäre Tumoren und tumorähnliche Bildungen der Papilla nervi optici, Klin. Monatsbl. Augenh. **55**:313, 1915.

7. Speciale-Cirincione: Sul sarcoma del disco ottico, Ann. ottal. e clin. ocul. **53**:849, 1925.

8. Oguchi, T.: Über einen Fall von Melanosarkom der Sehnervenpapille, Arch. Ophth. **130**:427, 1933.

9. Levine, J.: Primary Melanosarcoma of the Optic Disk, Arch. Ophth. **14**:229, 1935.

10. Cordes, F. C., and Hogan, M. J.: Primary Malignant Melanoma of the Optic Disc: Report of Case, Am. J. Ophth. **32**:1037, 1949.

11. Fry, W. E., and DeLong, P.: Tumor Formation at the Disc., Tr. Am. Ophth. Soc. **40**:325, 1942.

12. Cosmettatos, G. F.: Sarcome primitif du nerf optique, Rev. gen. ophth. **37**:5, 1923.

13. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 3, St. Louis, C. V. Mosby Company, p. 3095.

14. Bucalossi, A.: Su di un sarcoma della papilla ottica, Ann. ottal. e clin. ocul. **63**:676, 1935.

15. Reese, A. B.: Pigmentation of the Optic Nerve, Arch. Ophth. **9**:560, 1933.

16. Duke-Elder, W. S.,[13] p. 2486.

17. Wilder, W. H.: Melanotic Sarcoma of the Orbit, J. A. M. A. **35**:1362, 1900.

18. Willis, R. A.: The Spread of Tumours in the Human Body, London, Butterworth & Co., Ltd., 1952, p. 146.

19. Willis,[18] p. 214.

20. Rönne, H.: On Diagnosis of Choroidal Melanosarcoma, Tr. Ophth. Soc. U. Kingdom **56**:270, 1936.

21. Friedenwald, J. S.: Melanoma of the Choroid and Allied Tumors, in Penfield, W., Editor: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932.

22. Ophthalmic Pathology,[2] p. 399.

23. Wilder, H. C., and Paul, E. V.: Malignant Melanoma of the Choroid and Ciliary Body: Study of 2,535 Cases, Mil. Surgeon **109**:370, 1951.

NOTCHING OF THE OPTIC CHIASM BY OVERLYING ARTERIES IN PITUITARY TUMORS

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TUMORS at the optic chiasm may produce defects in visual fields by interruption of blood supply, by direct pressure of the tumor, or by forcing the optic nerves or chiasm against firm neighboring structures, such as the margins of the optic canals or the arteries of the circle of Willis. The last circumstance appears to account for many of the defects in the lower portion of the field encountered relatively late in the course of tumors in this region. On the other hand, the upper bitemporal hemianopsia that appears early may be attributed to direct pressure against the anterior margin of the chiasm and interference with its blood supply.

SURVEY OF LITERATURE

Notching of the optic nerves at their junction with the chiasm by arteries of the circle of Willis was recognized by Türck [1] a century ago. His description may be translated as follows:

> In the corpse of a blind person we found a neoplasm of the hypophysis nearly the size of a hen's egg, which had ruptured through the diaphragm formed by the periosteum of the sella turcica, and thus lay directly on the bones. The optic chiasm was notably flattened and was lifted forward and upward by the neoplasm. Both optic nerves were transversely grooved near their junction with the chiasm by the anterior cerebral arteries.
>
> As is well known, the chiasm lies within the circle of Willis at the base of the brain. As the optic nerves course forward from the chiasm to the optic canals, they leave the vascular circle by crossing its anterior segments, which are formed by the anterior cerebral arteries. This crossing takes place in such fashion that the transversely directed arteries come to lie above and the emerging optic nerves below. As a consequence, if the chiasm, as in our case, is elevated by a neoplasm, the attached optic nerves are indented transversely by the anterior cerebral arteries. Such intense compression had occurred that the attenuated segment of the left optic nerve consisted merely of an empty sheath, while at the corresponding portion of the right optic nerve the inner third or fourth of the nerve was preserved. Corresponding to this, there had been complete blindness of the left eye for several weeks prior to death and moderate loss of vision of the right eye.

In 1923, Fay and Grant [2] reported a case and reviewed the literature on the subject up to that time. This was the last comprehensive review in the English language. Lillie,[3] in 1931, recorded four cases in a candidate's thesis prepared for

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the American Ophthalmological Society. Balado and Malbrán,* in 1933, published two detailed studies from Argentina; these reports included splendid illustrations and extensive bibliographies. A few scattered reports of isolated cases have appeared in recent years.†

ANATOMIC ASPECTS

The usual structure of the circle of Willis is illustrated in Figure 1. Its variability is well recognized and has been described adequately by a number of investigators, notably Windle,[8] Fawcett and Blachford,[9] and de Schweinitz.[10] The anterior cerebral arteries commonly pass across the optic nerves near the junction of the

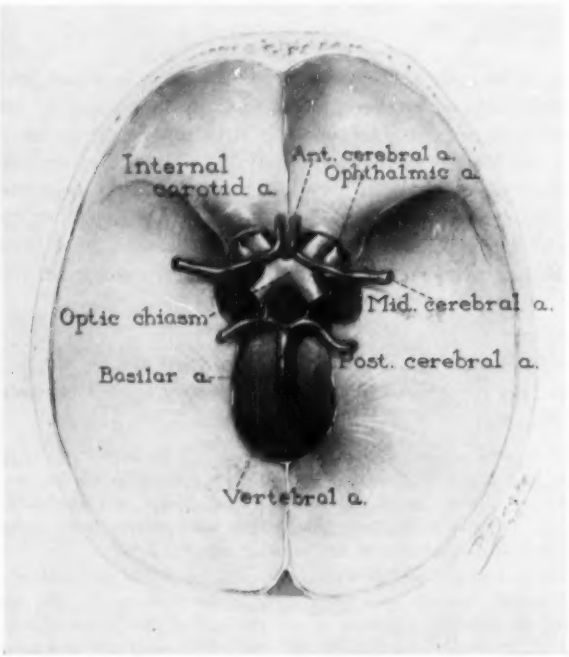

Fig. 1.—The optic chiasm and circle of Willis. Reproduced with permission of the publishers from Craig, W. McK.: Tumors of the Hypophyseal Region, in Bancroft, F. W., and Pilcher, Cobb: Surgical Treatment of the Nervous System, Philadelphia, J. B. Lippincott Company, 1946, pp. 176-203.

latter with the chiasm; these arteries are united by the anterior communicating artery. Occasionally the chiasm lies farther forward and is itself in contact with these arteries; asymmetry of the vessels may distort the ordinary relationships. When a tumor of the pituitary body lifts the optic chiasm up against the anterior half of the circle of Willis, the anterior cerebral arteries do not give way freely but are pulled taut between the internal carotid arteries and come to lie directly across

* References 4 and 5.

† References 6 and 7.

the optic chiasm. The chiasm is squeezed between the tightly drawn arteries and the tumor. The slow, progressive penetration of vessels into the nerve tissue is caused by direct pressure and also by the constant pounding of the arterial pulse.[11]

REPORT OF CASES

From material at our disposal, we have selected a few representative cases of pituitary tumors accompanied by notching of the optic nerves or chiasm by arteries of the anterior part of the circle of Willis.

CASE 1.—A 59-year-old man requested an examination of his eyes, stating that for 10 years he had been unable to secure satisfactory glasses. Three years previously an oculist had told

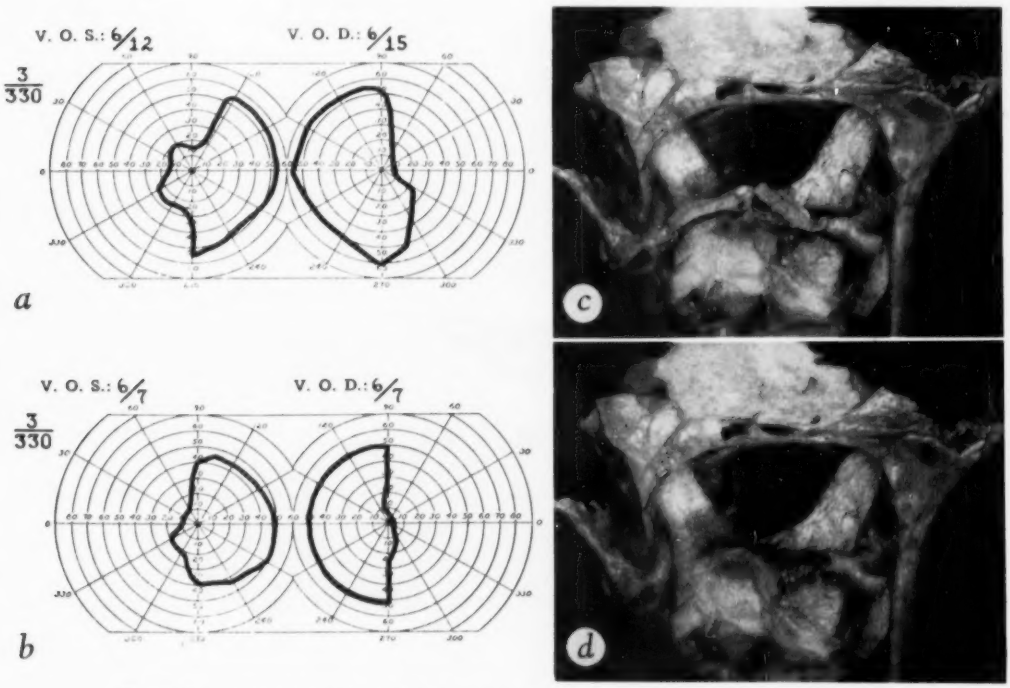

Fig. 2 (Case 1).—(*a*) Visual fields showing incomplete bitemporal hemianopsia with some sparing of the central portions of the temporal halves. (*b*) Five months later; almost complete bitemporal hemianopsia. (*c*) Chiasmal region at necropsy. In the upper portion can be seen part of the body of the sphenoid, the tuberculum sellae, and the optic foramina. The black region between the optic nerves represents clotted blood lying within the sella turcica. An internal carotid artery lies on either side of the chiasm. (*d*) Notching of the chiasm produced by the overlying anterior cerebral arteries.

him that, although his eyes appeared normal, his vision was not good and suggested that he consult his family physician. The patient did not do this. During the two months prior to admission, he had noted further deterioration in visual acuity and loss of ability to see to the sides.

On examination, visual acuity of the right eye was recorded as 6/15; that of the left was 6/12. Ophthalmoscopy disclosed mild pallor of the right optic disk and a suggestion of pallor of the left. Study of the perimetric fields showed incomplete bitemporal hemianopsia (Fig. 2*a*).

Roentgenograms of the head revealed great enlargement of the sella turcica, with destruction of its floor and of the posterior clinoid processes. The diagnosis was intrasellar tumor with suprasellar extension. Surgical removal of the tumor was advised, but the patient preferred to wait.

When he returned, five months later, further loss was apparent in the temporal halves of the visual fields (Fig. 2*b*), although central acuity was recorded as being somewhat improved. The neurosurgeon performed transfrontal craniotomy and encountered a large chromophobe adenoma lying anterior to the optic chiasm; the tumor was removed completely. Two days later, after experiencing fever and intense headache, the patient died.

At necropsy, the chiasm and some of its neighboring structures were removed in a single intact specimen. Lying across the superior surface of the anterior portion of the chiasm could be seen the anterior cerebral arteries joined by the short anterior communicating artery

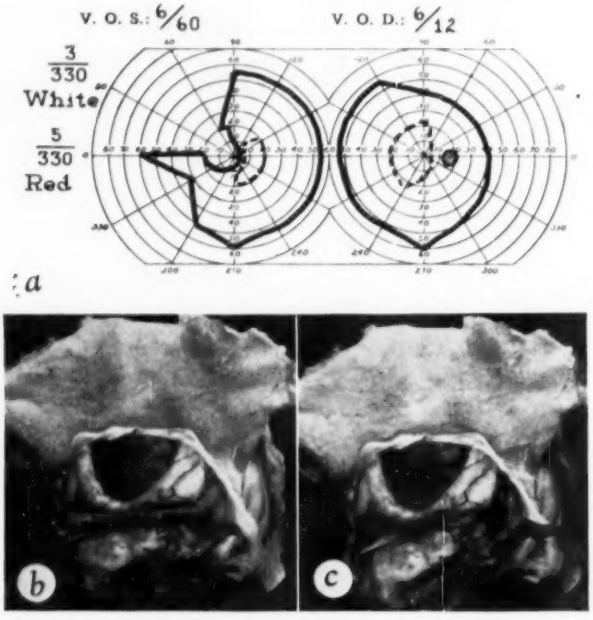

Fig. 3 (Case 2).—(*a*) Visual fields showing bitemporal hemianopsia, with much greater loss in the left eye than in the right. (*b*) Chiasmal region at necropsy. In the upper part is the body of the sphenoid. The dark semicircular region at the center represents pituitary adenoma. On either side of it is an optic nerve, and behind it is the chiasm. (*c*) Transverse notching produced by the anterior cerebral and anterior communcating arteries.

(Fig. 2*c*). When these arteries were removed, a deep notch was visible in the anterior portion of the chiasm (Fig. 2*d*). The notch appeared to be deep enough to account for interruption of most of the crossing fibers of the chiasm and for the consequent loss of vision in the temporal fields.

Case 2.—A 44-year-old woman complained of blurring of her left eye for 6 weeks and of her right eye for 10 days. She had not menstruated for two years.

On examination, visual acuity of the right eye was found to be 6/12; that of the left was 6/60. Ophthalmoscopic examination disclosed pallor of both optic disks. Charting of the perimetric fields demonstrated bitemporal hemianopsia (Fig. 3*a*), with relatively moderate loss in the field of the right eye; in the field of the left eye was a dense temporal defect that had involved the central zone. The roentgenologist reported destruction of the floor of the sella turcica and of the posterior clinoid processes. The diagnosis was that of pituitary tumor.

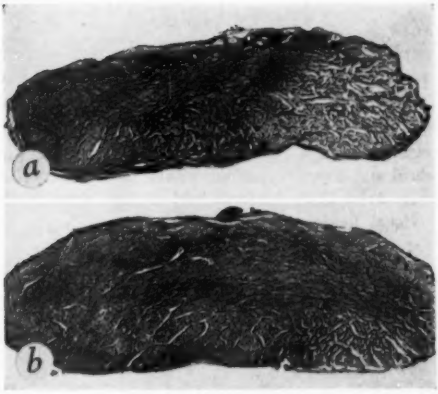

Fig. 4 (Case 2).—(*a*) Left optic nerve; note compression and flattening. Almost complete degeneration of the myelin sheaths is present in the medial third; this extends along the lower two-thirds, which was the part in contact with the capsule of the pituitary tumor. The connective tissue remains intact, but because of the degeneration it is slightly condensed. (*b*) Right optic nerve; this is also compressed and partially flattened. Myelin degeneration is much less and is practically limited to a small portion of the inferior and lateral quarter of the nerve, where the structure appears loose. The stroma is almost normal. Both, Weigert stain; × 12.

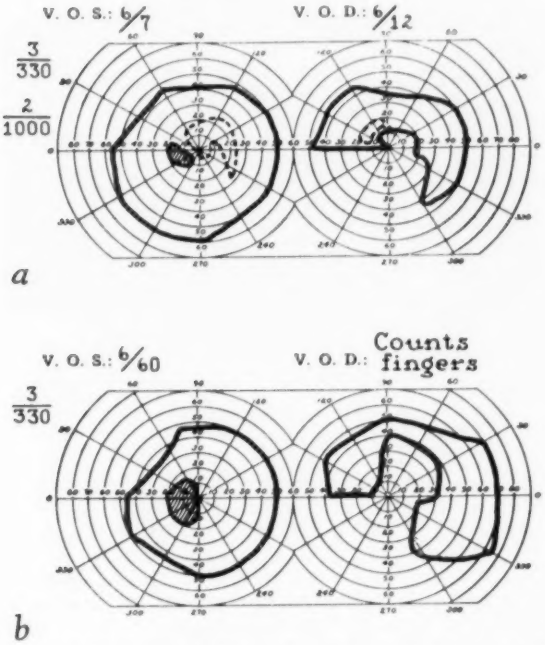

Fig. 5. (Case 3).—(*a*) Visual fields showing inferior altitudinal anopsia, more advanced in the right eye than in the left. (*b*) Progression of the defects in the fields after one year.

The neurosurgeon performed transfrontal craniotomy and encountered an encapsulated chromophobe adenoma, which was the size of an English walnut, lying between the optic nerves and forcing the chiasm dorsally and posteriorly. A small portion of the tumor was removed. Two days later the patient died.

At necropsy, the chiasm and some of its neighboring structures were removed in a single piece. The anterior cerebral and anterior communicating arteries were situated across the upper surface of the chiasm (Fig. 3*b*). Their presence had created a notch (Fig. 3*c*). In conformity with the defects in the visual fields, the notching was much deeper on the left side than on the right. Sections of the optic nerves are shown in Figure 4*a* and *b*.

CASE 3.—A 39-year-old man complained of pain behind the right eye and of impaired vision. For two and a half years he had suffered from frequent occipital headaches. About a year

Fig. 6 (Case 3).—Base of brain. Near the center, in the region posterior to the frontal lobes and between the temporal lobes, is the space which the pituitary tumor had made for itself. Note the great distance between the cut ends of the internal carotid arteries, together with the lengthened course of the anterior cerebral arteries between their points of origin at the internal carotids and the point of origin of the anterior communicating artery.

prior to admission diplopia appeared; this had persisted for several months, and glasses had been prescribed for it. Vision of the right eye had been impaired for six months, and for one month pain had been present behind the right eye, accompanied by a considerable degree of photophobia.

The visual acuity of the right eye was 6/12; that of the left was 6/7. Ophthalmoscopic examination disclosed intense pallor of the right optic disk and moderate pallor of the left. The abducens nerve on the right side was completely paralyzed; that on the left side was affected slightly. Sensation of the face was normal. A chart of the visual fields (Fig. 5*a*) showed an inferior altitudinal anopsia, with much greater loss in the field of the right eye than in the left, indicative of involvement of the upper portion of both optic nerves that was

more extensive in the right nerve than in the left. Roentgenologic examination disclosed extreme enlargement of the sella turcica, with destruction of its floor and the posterior clinoid processes. The patient's skin was lemon-yellow, soft, and pale, and his beard was so scanty that he shaved only twice a week. Blood pressure was 100 mm. of mercury systolic and 70 mm. diastolic. The diagnosis was that of a large intrasellar tumor. Treatment with roentgen rays was advised and administered.

The patient returned a year later complaining that his vision had deteriorated still further and that his headaches were intense. The defects in the visual fields had increased (Fig. 5*b*). Blood pressure was 94 mm. of mercury systolic and 62 mm. diastolic. Operation was advised and accepted by the patient in spite of the great risk entailed. The neurosurgeon found a large

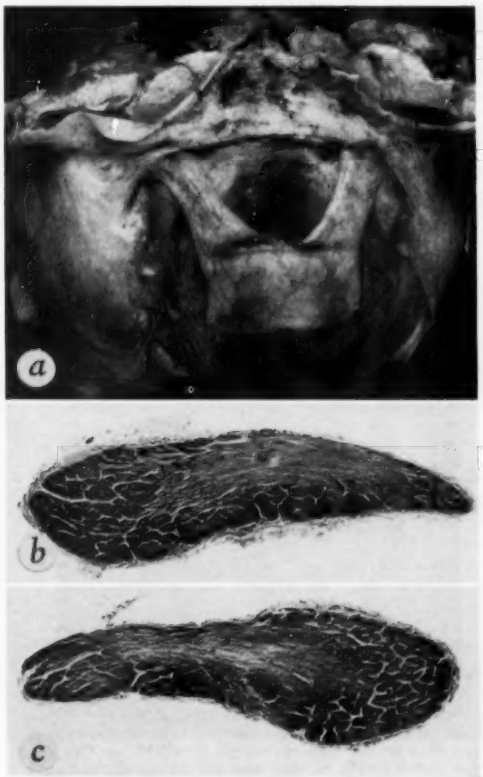

Fig. 7 (Case 3).—(*a*) Large, rounded pituitary tumor. Overlying it is the optic chiasm, from which the optic nerves pass forward to enter the optic canals. A portion of an internal carotid artery is visible on the lateral aspect of each optic nerve. Passing transversely across the anterior portion of the chiasm is a notch cut by the anterior cerebral and communicating arteries. (*b*) Left optic nerve; it is greatly flattened and distorted by the pressure of the tumor. The degeneration of the myelin sheaths is readily seen in the most flattened portion in the upper half and medial third. This portion stains less darkly, owing to loss of myelin. The lateral portion and the inferior third stain in a relatively normal manner. (*c*) Right optic nerve; it is also flattened and distorted. The lateral fourth stains in a relatively normal manner, while almost complete degeneration of the myelin sheaths is noted in the remaining portion. In one small segment beneath the inferior portion of the nerve sheath, some intact myelin sheaths are present. In the degenerated zone, the connective tissue is condensed. (*b* and *c*) Weigert stain; × 12.

pulsating mass that looked so much like an aneurysm that he made no attempt to remove it. The patient died suddenly 12 hours after returning from the operating room.

At necropsy a large cystic adenoma of the pituitary body was demonstrated. It had spread apart the internal carotid arteries and lengthened the anterior cerebral arteries in their course between their origin at the internal carotid arteries and the point at which the anterior communicating artery arose (Fig. 6). The tumor had caused horizontal notching of the anterior border of the optic chiasm by the anterior cerebral arteries (Fig. 7*a*). Sections of the optic nerves are shown in Figure 7*b* and *c*.

Case 4.—A 42-year-old woman complained of progressive failure of vision during the preceding two months. For four months she had suffered frequent headaches and had tired easily. Her last menstrual period had occurred six years previously, at the age of 36.

Visual acuity was found to be about 6/60 in each eye. Ophthalmoscopic examination disclosed mild pallor of both optic disks. Perimetry did not give entirely satisfactory results, but it did

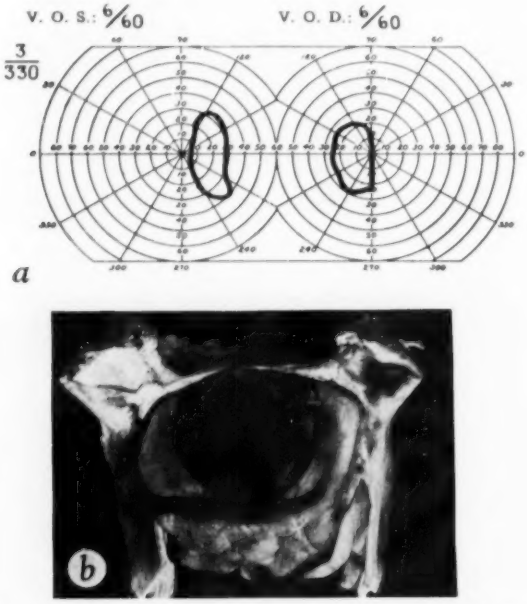

Fig. 8 (Case 4).—(*a*) Visual fields, showing bitemporal hemianopsia and generalized contraction of the remaining nasal halves. (*b*) Specimen at necropsy. In the upper part is the thinned anterior wall of the sella. On either side of the dark tumor in the center is an optic nerve passing backward to join the chiasm, which is visible in the lower part. A deep notch crosses each optic nerve transversely, cutting the left nerve more deeply than the right.

demonstrate bitemporal hemianopsia with contraction of the nasal halves of the visual fields; these findings indicated a lesion at the optic chiasm (Fig. 8*a*). Roentgenologic study of the head revealed almost complete destruction of the sella turcica by a large intrasellar tumor.

The neurosurgeon performed transfrontal craniotomy and found a huge cystic chromophobe adenoma, of which he was able to remove only a small part. He noted that the right optic nerve was flattened and that it was constricted at the superior margin of the optic foramen. The patient died three days later.

At necropsy the tumor and the overlying optic nerves and chiasm were removed in a single piece. Deep notching was present in the left optic nerve at its junction with the chiasm (Fig. 8*b*). The right optic nerve was lightly notched and was pressed firmly against the upper margin of the optic foramen.

CASE 5.—A 56-year-old man complained of blindness of his left eye. He stated that vision of the left eye had become blurred one year previously; about a month later the eye suddenly became blind. At the same time he had noted an intense headache, which had lasted several days. On being questioned, he admitted intolerance to cold for two years and loss of strength and potency.

On examination, the acuity of the right eye was 6/12 and its field was contracted temporally; the left eye was blind (Fig. 9*a*). The optic disks were pale, and the left third cranial nerve was paralyzed. Roentgenograms of the head disclosed great enlargement of the sella turcica

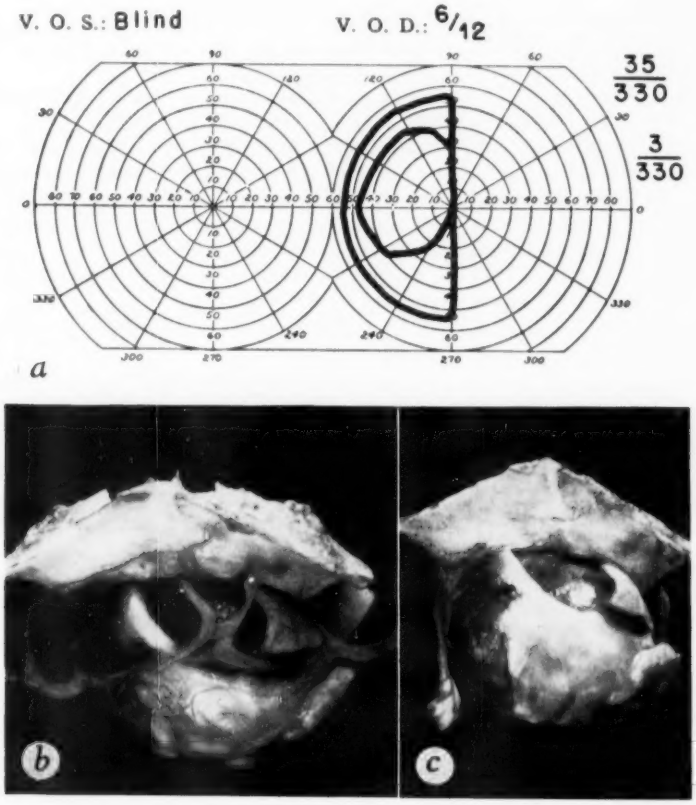

Fig. 9 (Case 5).—(*a*) Visual fields; the left eye is blind, and the field of the right eye exhibits loss of its temporal half. (*b*) Above is the tuberculum sellae turcicae; below it lies the dark tumor, between the optic nerves; farthest below is the chiasm. (*c*) Grooves produced by the overlying arteries.

by an intrasellar tumor, with suprasellar extension. The clinical diagnosis was chromophobe adenoma of the hypophysis.

The neurosurgeon performed transfrontal craniotomy and encountered a huge cystic mass containing blood; this mass was situated between the optic nerves. He was unable to determine whether it was an aneurysm or hemorrhage into a pituitary tumor; no attempt at removal was made. The patient died two days later.

At necropsy, the tumor and overlying structures were removed. The position of the anterior cerebral arteries and the grooves in the chiasm produced by them are shown in Figure 9*b* and *c*.

SUMMARY

Five cases have been selected to demonstrate that tumors of the hypophysis may press the optic nerves and chiasm upward against arteries of the fore part of the circle of Willis and thereby produce a transverse notching in the chiasm or nerves. This notching may be responsible for defects in the visual fields associated with hypophyseal tumors, especially losses in the lower quadrants of the fields that occur during the middle and late stages of growth of the tumor.

REFERENCES

1. Türck, L.: Über Compression und Ursprung des Sehnerven, Ztschr. k.-k. Gesellsch. Aertz. in Wien **8**:299-304, 1852.

2. Fay, T., and Grant, F. C.: Lesions of the Optic Chiasm and Tracts with Relation to the Adjacent Vascular Structures, Arch. Neurol. & Psychiat. **9**:739-750, 1923.

3. Lillie, W. I.: Study of the Pathologic Changes in the Optic Nerves and Chiasm in Comparison with Changes in the Visual Field in Association with Large Pituitary Tumors, Tr. Am. Ophth. Soc. **29**:433-444, 1931.

4. Balado, M., and Malbrán, J.: Contribución a la estructura del quiasma óptico humano (hemianopsia binasal; estudio anátomo-clínico), Semana méd. **2**:797-807, 1933.

5. Balado, M., and Malbrán, J.: Compressión y sección del quiasma por las arterias del polígono de Willis, Arch. argent. neurol. **9**:126-133, 1933.

6. Prskavec, F.: Über einen Fall von Sehnervenatrophie durch Gefässdruck bei Hypophysentumor, Klin. med. **2**:1024-1028, 1947.

7. Trumble, H. C.: Pituitary Tumours: Observations on Large Tumours Which Have Spread Widely Beyond the Confines of the Sella Turcica, Brit. J. Surg. **39**:7-24, 1951.

8. Windle, B. C. A.: On the Arteries Forming the Circle of Willis, J. Anat. & Physiol. **22**:289-293, 1888.

9. Fawcett, E., and Blachford, J. V.: The Circle of Willis: An Examination of 700 Specimens, J. Anat. & Physiol. **40**:63-70, 1905.

10. de Schweinitz, G. E.: Concerning Certain Ocular Aspects of Pituitary Body Disorders, Mainly Exclusive of the Usual Central and Peripheral Hemianopic Field Defects, Tr. Ophth. Soc. U. Kingdom **43**:12-109, 1923.

11. Malbrán, J.: El campo visual en los procesos quiasmáticos, Semana méd. **1**:569-593, 1934.

RADIOACTIVE PHOSPHORUS AS A DIAGNOSTIC AID IN OPHTHALMOLOGY

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RADIOACTIVE phosphorus (P^{32}) was first used as a diagnostic aid in the detection of breast tumors by Low-Beer in 1946.[1] It was subsequently used to aid in localization of brain tumors by Selverstone and associates.[2]

In March, 1952, Thomas, Krohmer, and Storaasli[3] published the first report on the detection of intraocular tumors with radioactive phosphorus. The technique used, in brief, was as follows:

> Five hundred microcuries of P^{32} in the form of sodium biphosphate (sodium acid phosphate) in sterile isotonic saline was injected intravenously in patients with suspected intraocular tumors. Tetracaine drops were instilled in each eye for local anesthesia. Counts were made with a small Geiger-Müller tube over the area of the suspected tumor and in other areas of the same eye and on the other eye. The counts were made at intervals of one-half hour, one hour, and one and one-half hours after the injection of P^{32}.

The dose of 500 μc of P^{32} was selected because it is below the level of radioactivity which might produce injurious effects. It is relatively twice the accepted tolerance level, but Thomas and associates did not consider this a significant hazard. The dose is high enough that sufficient counts can be obtained within a reasonable length of time to give statistically significant results without undue strain on the patient or the examiner.

The preliminary results which these investigators presented were remarkably good. They reported eight cases in which radioactive phosphorus was injected, in six of which the tumors were melanomas. In each of these six was demonstrated a definite difference in the count over the tumor and the count obtained over tumor-free areas, either in the same eye or in the opposite eye. One of the remaining two cases was of an iris cyst, and, as might be expected, no difference was obtained in the count over the cyst and that over the other areas. In the other case the lesion clinically appeared to be a melanoma, but no difference in the count was found over the area of the supposed tumor and normal areas. Five ophthalmologists agreed that the eye contained a malignant tumor. The eye was removed, but no tumor was present. The test with radioactive phosphorus gave the correct answer; the five ophthalmologists were wrong! This study gave the definite impression that the test with radioactive phosphorus was a real diagnostic aid. However, this preliminary report neglected the most fundamental scientific observations, some of which reduce the reliability of this test. It is the purpose of the present paper to point out these fundamental observations.

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When radioactive phosphorus is injected intravenously, it spreads through the blood stream. In the eye, it is present in greatest concentration in the uveal tract and the rectus muscles soon after the injection. The phosphorus then diffuses into the tissue and is slowly removed from the blood stream. This diffusion was carefully studied by Haigh and Reiss [4] and is well expressed by the curve shown in Figure 1, which was adopted from their article.

In the curve in Figure 1 the radioactivity shows a rapid increase from 0 to 0.5 minute and then a rapid fall up to four minutes. This part of the curve (*A*) represents mixing of the tracer in the blood volume before loss by diffusion through the capillary walls becomes marked. In part *B*, lasting from 4 to 15 minutes after injection, there is both mixing of the tracer with the blood and appreciable diffusion through the capillary walls. Part *C* represents solely the rate of removal of the tracer from the blood.

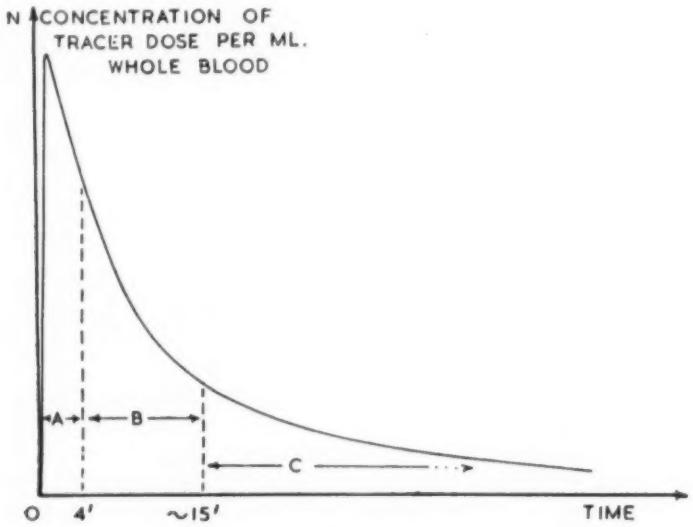


Figure 1

Our own work gave results corresponding closely to that of Haigh and Reiss. A group of patients with normal eyes who were treated for polycythemia vera with large doses of P^{32} were studied. Counts over the normal uveal tracts were started with the injection of P^{32} and continued for approximately one hour. The count rose rapidly for the first 15 minutes, at which time it reached a plateau, and leveled off only slightly for an hour after the injection. Comparable rises and very slow falling off of the counting rate were demonstrated in patients with melanomas. The rapid rise is due to the fast distribution of the radioactive phosphorus throughout the vascular tree, and the slow fall is associated with withdrawal of the P^{32} from the blood vessels into the surrounding tissues.

The vascular supply of the eye is greatest in the extraocular muscles and the uveal tract. Unlike other organs, the central portion of the eye (aqueous, lens, and vitreous) is entirely avascular. As would be anticipated, the P^{32} easily reaches a

high concentration in the extraocular muscles and uveal tract, but remains in higher concentration in these structures long after the injection, unlike other organs. The distribution of P^{32} in the various structures of the eye is shown in Table 1.

The figures in Table 1 were compiled from data obtained by quickly freezing an eye in a mixture of acetone and solid carbon dioxide (dry ice) 45 hours after injection of 100 μc of P^{32} intravenously. After the eye was quickly frozen to prevent

TABLE 1.—*Distribution of P^{32} in Various Ocular Structures*

Material	Activity in Counts per Second per Gram of Tissue
External ocular muscle	180.0
Choroid and retina	86.0
Ciliary body	72.0
Cornea	27.0
Lens capsule and cortex	15.8
Aqueous	6.0
Sclera	2.0
Vitreous	1.0
Lens nucleus	0.9

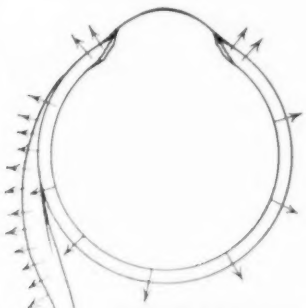


Figure 2

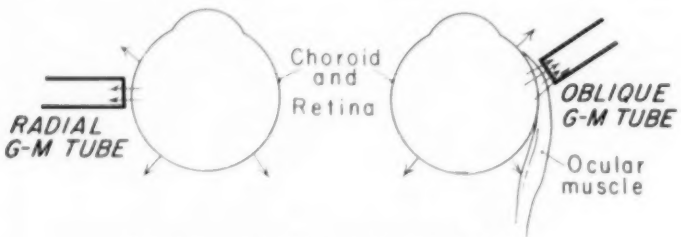
diffusion of P^{32}, the eyeball was dissected into its component parts. The figures in Table 1 demonstrate that the activity determined by a Geiger-Müller tube held over a normal eye 48 hours after the injection of P^{32} is still determined by the response from the uveal tract and the rectus muscles, and to a very slight extent by the other parts of the eyeball. Accordingly, we may look upon the normal eye as behaving like a hollow sphere so far as response to the counting test is concerned. This is demonstrable in Figure 2.

The vitreous, aqueous, lens, and sclera are relatively inert and take up very little P^{32}; consequently, the count is obtained almost entirely from the P^{32} in the uveal tract and retina, unless the tube is held over a rectus muscle. If a tube is

held over a rectus muscle, the count is increased approximately 70% as compared with the count obtained by holding the tube in an area between the rectus muscles, but over the uveal tract. In light of the fact that a malignant melanoma only increases the count from 25 to 300% as compared with the normal area, it can readily be seen that the presence of a rectus muscle under the counting tube can produce a greater change than a melanoma.

If the counting tube is held perpendicular, with its rim touching the globe, only the beta rays directly under it can enter. However, if the tube is turned so as to point backward toward the macula, the beta rays from a much greater section of uveal tract, as well as some particles from orbital fat, may enter the tube and increase the count. This is illustrated in Figure 3.

Figure 3 demonstrates that an increase in count will result if the tube is pointed backward toward the macula. It shows that the tube is held at an angle, approaching tangential in some instances, in trying to get a count on a presumptive tumor far toward the posterior pole. This opens the window of the tube to receive beta



EFFECT OF POSITION
OF GEIGER-MÜLLER TUBE

Figure 3

rays from tissues outside the eyeball and from an area of choroid which is larger than the area of the window. This gives an indeterminate increase in the counting rate, so variable, in fact, that comparison with normal areas becomes unreliable.

It has been demonstrated that almost the entire count is obtained from the uveal tract, unless the counting tube is held over a muscle. A variation in the count will be obtained, depending upon whether the tube is held in contact with the sclera or some distance away from it. There is not a progressive falling off in the counting rate as the tube is held at progressively greater distances from the sclera, as one would expect. As the tube is held at progressively greater distances from the sclera, there is first an increase, then a decrease, in the count. This phenomenon is explained by the fact that the beta rays coming from the side of the tube cannot gain entry into it if the tube is in contact with the sclera. If the tube is held 2 or 3 mm. away from the sclera, these beta rays are admitted to the tube and increase the counting rate. This effect is marked for the first few minutes after the P^{32} injection, while the activity is still well confined to the blood vessels. It fades as the P^{32} diffuses, until the paradox is no longer demonstrable after 15 minutes or so.

Figure 4 illustrates how the counting rate is increased by withdrawing the tube from the sclera. In Figure 4 *a* the tube is in contact with the sclera, and all rays

coming from points not directly under the tube are excluded from entry by the side wall of the tube. In Figure 4 *b* these rays are admitted as the tube is pulled away from the sclera a few millimeters. In Figure 4 *c* there is again a decrease in the count as the tube is pulled still farther away from the sclera.

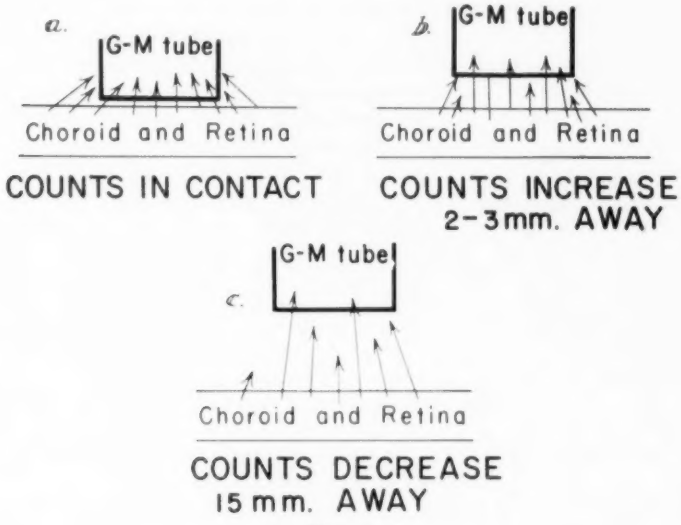


Figure 4

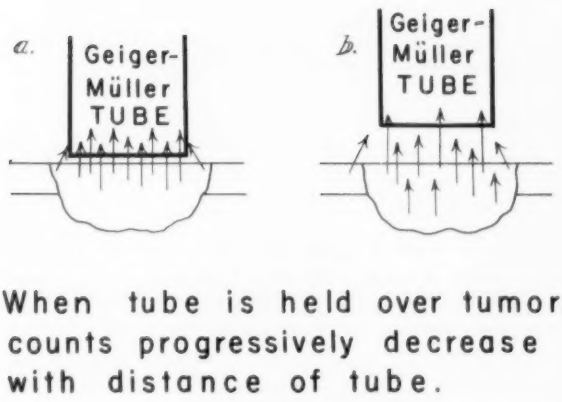


Figure 5

If the counts are coming from a tumor instead of a thin layer of radioactive tissue, there is a progressive falling off with withdrawal of the window away from the surface because the accessions from the sides are offset by deletion from the depths. This is readily demonstrated by noting the change in counting rate as the tube is removed from contact with the tongue or lips.

The difference between the falling-off rate obtained in the count over a normal uvea and that obtained over a uvea thickened as by tumor tissue can be demonstrated both experimentally and clinically.

A hollow double-walled glass shell was constructed and filled with P^{32}. On one side the shell was so thin that it contained a layer of P^{32} less than 1 mm. thick. On the other side, the shell contained a layer of P^{32} 5 mm. thick. This shell is diagrammed in Figure 6.

When the counting tube was held in contact with the thin position of the shell and then removed to progressively greater distances, the rate first increased and

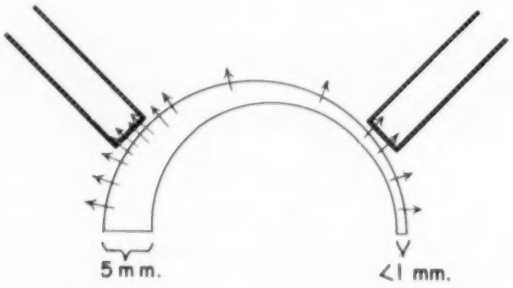


Figure 6

TABLE 2.—*Counts Obtained Over Shell Containing P^{32}* *

Tube held in contact over thin area	100%
Tube 2 mm. away	115%
Tube 5 mm. away	120%
Tube 10 mm. away	178%
Tube held in contact over thick area	100%
Tube 2 mm. away	85%
Tube 5 mm. away	83%
Tube 10 mm. away	60%

* Rate of count when held in contact was taken as 100%.

then decreased. However, when the same maneuver was executed over the thick portion of the shell, the counting rate progressively decreased. This is demonstrated in Table 2.

The same phenomenon was observed clinically in Table 3. The falling-off rate over the normal side of an eye is compared with that over a tumor.

From the discussion already presented, it is evident that the counting rate obtained after injection of P^{32} will vary with the following factors: (1) dose of P^{32}, (2) length of time elapsed since injection, (3) whether or not the counting tube is held over a muscle, (4) whether or not the tube is held perpendicular to the surface of the globe, and (5) whether or not the tube is pressed against the sclera in close contact.

Still other variables are present, however. The vascularity of the tumor, if one is present, will cause a great variation in the count. This was demonstrated in a patient with a very extensive melanoma which had broken through the sclera anteriorly. A portion of the melanoma was extremely vascular; this gave a very high count. Another portion was much less vascular; this gave a relatively low count. A comparison of the vascular area and the less vascular area, the opposite eye, and the tongue is shown in Table 4. It will be observed that the vascular area was 2 to 2.8 times as active as the less vascular area. The activity over the vascular area was approximately equal to that over the tongue. The less vascular area was only slightly more active than the normal eye; yet the vascular area was approximately three times as active as the normal eye.

TABLE 3.—*Average Count Obtained Over Tumor Eyes* *

	Over Normal Eye	Over Melanoma
Tube held in contact	100%	100%
Tube held 3 mm. away	110%	92%
Tube held 5 mm. away	108%	76%
Tube held 8 mm. away	102%	63%
Tube held 15 mm. away	77%	49%

* Rate of count when tube was in contact was taken as 100%.

TABLE 4.—*Activity (Counts per Second) in Vascular and Nonvascular Areas of Tumor, Tongue, and Normal Eye*

Vascular Area of Tumor	Nonvascular Area of Tumor	Tongue	Normal Eye
12-15	4.5-7.5	5.4	4.4

TABLE 5.—*Rates of Counts Over Eye Containing Large Retinoblastoma and Normal Eye of Same Patient (in Counts per Second)*

	Normal Eye	Retinoblastoma Eye
15′ after injection	4.2/sec.	3.7/sec.
20′ after injection	3.9/sec.	3.8/sec.
50′ after injection	5.6/sec.	5.9/sec.

Counts obtained for a child with an extensive retinoblastoma demonstrated a statistically significant decrease in the counting rate over the tumor as compared with the counts over the noninvolved eye for the first 15 minutes after injection. This corresponds to parts *A* and *B* of Haigh and Deiss's curve, shown in Figure 1. It was felt that this low count was the result of the relative avascularity of the tumor. After 50 minutes the counts over corresponding areas in the two eyes were essentially the same, perhaps due to the ability of the tumor tissue to retain P^{32}.

In light of the fact that the count varies so greatly with the vascularity, it is to be expected that lesions other than tumor will increase the counting rate if they influence the vascular supply. An inflammation results in a great increase in the counting rate. This was demonstrated experimentally as follows:

An inflammation was produced in one eye of a rabbit by the injection of turpentine into the anterior chamber. P^{32}, 100 μc, was injected into the animal. The

counting rate over the inflamed eye was almost three times as great as that over the noninflamed eye and equal to that of the tongue, as shown in Table 6.

There is reason to believe that a much more accurate differential counting rate would be obtained if the counts were made not from one to one and a half hours after injection but after much longer time intervals. During the first 15 minutes after injection the phosphorus is largely free in the blood stream. During the remainder of the first hour it is diffusing into the tissues. Phosphorus in the tissues is found combined with carbohydrates, fats (phospholipids), and proteins. In general, in most tissues studied, the combination of radioactive phosphorus is evident first in the carbohydrate moiety, second in the fat portion, and third in the protein.[5] The P^{32} in carbohydrate reaches a state of equilibrium in about an hour, whereas the nucleoprotein P^{32} may take up to 48 hours. The type of tissue being observed, as well as their physiological state, may change the uptake of P^{32} considerably.

If the count obtained is to demonstrate the rapidity of the growth of the tissue, then we wish to count the phosphorus bound with proteins. It is the phosphorus bound with proteins that is found in nuclei in greatest concentration, and more nuclei are found with more rapidly growing tissue. The protein-bound phosphorus is present in greatest concentration long after the injection, and hence counts made

TABLE 6.—*Counts Over Inflamed Eye, Noninflamed Eye, and Tongue of Rabbit, Given in Average Counts per Second*

Inflamed Eye		Noninflamed Eye		
Tube over Cornea	Tube over Sclera	Tube over Cornea	Tube over Sclera	Tongue
6.6/sec.	10.5/sec.	3.0/sec.	4.2/sec.	10.6/sec.

days, rather than hours, after the injection would probably be more profitable. There would be difficulty, however, with the greatly lowered activity with such long times.

SUMMARY

Counts of radioactivity after the injection of radioactive phosphorus are subject to many variables. Some of these variables are easily controlled and are found with any organ, whether it be brain, breast, or eye. Such variables are the dose of P^{32} and the length of time since injection.

Other variables are dependent on the fact that the eyeball acts as a hollow sphere as far as radioactivity is concerned; only the vascular tissues produce any great radioactive response. Because of this fact, the count is normally obtained from a very thin layer of tissue—the vascular uveal tract. Should the tube be held over a rectus muscle, the thickness of vascular tissue under the counter is greatly increased, and, because of this, the count is increased. If the counting tube is pointed backward toward the macula, the tube receives impulses from a much greater length of uveal tissue and extraocular tissues, and thus the count is increased.

The "hollow-sphere effect" accounts for an increase in counting rate as the tube is removed away from the eyeball before the count begins to fall off. With a thicker radioactive tissue present below the tube, such as a tumor, there is no preliminary increase in count, but only a continuous falling off of the count.

Variations due to vascularity are also encountered if a tumor is present. Not only does the counting rate vary with the vascularity in different tumors, but it will

cause variations in different areas within the same tumor. The more vascular areas within the tumor produce much faster counts than less vascular areas within the same tumor. Very avascular tumors, such as a retinoblastoma, may actually produce a slower counting rate than that found over the normal eye.

As would be expected an inflammation which increases the blood supply to the eye likewise results in much greater radioactivity and could give the same response as, or a greater response than, a tumor. If the counts are performed a number of days after the injection, it is theoretically probable that a much more accurate differentiation between actively growing tissue, such as tumor, and other tissue simply with more blood flowing through it could be made.

CONCLUSIONS

The use of P^{32} in the diagnosis of tumors suffers from a number of physiological, anatomical, and physical difficulties, which we shall have to learn to overcome. A particular difficulty is posed by tumors near the posterior pole.

The use of radioactive phosphorus might be an extremely valuable diagnostic tool if (1) a counter were designed that could be applied directly over a tumor located near the posterior; (2) the variables outlined in this paper were carefully controlled, and (3) perhaps, the counts were made at much longer intervals after the injection.

Robert Newell, M.D., Professor of Biophysics, Stanford University School of Medicine, and Harold Loeb, Ph.D., made numerous cogent suggestions.

REFERENCES

1. Low-Beer, B. V. A.: Surface Measurements of Radioactive Phosphorus in Breast Tumors as a Possible Diagnostic Method, Science **104**:399 (Oct. 25) 1946.

2. Selverstone, B.; Solomon, A. K., and Sweet, W. H.: Localization of Brain Tumors by Means of Radioactive Phosphorus, J. A. M. A. **140**:277 (May 21) 1949.

3. Thomas, C.; Krohmer, J., and Storaasli, J.: Detection of Intraocular Tumors with Radioactive Phosphorus, A. M. A. Arch. Ophth. **47**:276 (March) 1952.

4. Haigh, C., and Reiss, M.: Diagnostic and Therapeutic Uses of Radioactive Isotopes: Symposium: Some Applications of I^{131} and Na^{24} to Clinical Diagnosis, Brit. J. Radiol. **23**:534 (Sept.) 1950.

5. Kamen, M.: Radioactive Tracers in Biology, Ed. 2, New York, Academic Press, Inc., 1951, pp. 179-201 and 279-299.

DACRYOCYSTOGRAPHY

I. The Normal Lacrimal Apparatus

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IT HAS been almost half a century (1909) since roentgenographic methods were first applied to the study of the lacrimal drainage apparatus. Since then, although many ophthalmologists have had experiences with these methods, there exist only a few isolated papers available as reference material in this field. Conspicuously deficient has been information concerning the appearance of the normal lacrimal system. Also, there is a lack of experience on the part of the clinical radiologist, and as a result the value of lacrimal x-rays has been limited.

This study had for its purposes (*a*) the development of a simple, standardized clinical method for the roentgen examination of the lacrimal apparatus; (*b*) the determination of roentgenographic criteria for the normal system; (*c*) the selection of a contrast medium, eminently suited for lacrimal roentgenography and hitherto unreported for this purpose, and (*d*) emphasis on the aid which this technique may afford the clinical ophthalmologist.

HISTORY AND REVIEW OF LITERATURE

In 1909, Ewing [1] first advocated the use of radiopaque material to outline pathologic nasolacrimal systems. Using a suspension of bismuth subnitrate in liquid petrolatum U.S.P. (Albolene), he demonstrated two abscessed lacrimal sacs and showed one example of the normal lacrimal canal.

In 1920 von Szily [2] described the pathology of the tear passages, visualized roentgenographically. Shortly thereafter Campbell and associates [3] presented case reports and results of roentgenographic visualization in 60 patients. They utilized a suspension of bismuth in oil and advocated taking a two-day follow-up film to reveal any retained dye. They noted a difference between the relatively narrow canal in white patients and the wider passageway in Negroes. They stressed the need for x-rays to determine the exact position of the obstruction in the lacrimal system. The latter point, they felt, was helpful to the surgeon in selecting the proper type of therapy.

Hourn [4] suggested placing dental x-ray film intranasally for visualization of the nasolacrimal passageways. He routinely irrigated with iodized oil U.S.P. (Lipiodol) solution through the punctum, but also advocated a retrograde injection up through the nasal ostium in cases of stenosis of the sac-duct junction. This produced many "technical difficulties and obstacles," he admitted, but his imagination and ingenuity should not go unnoticed.

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Spackman's review,[5] in 1938, of 100 patients examined over a period of four years is the most comprehensive paper to date. A mixture of iodized oil and olive oil was employed as the radiopaque medium. A brief illustrated review of the normal outline of the nasolacrimal passageways was presented, and there were several illustrations of pathologic outlines. Spackman felt that most clinicians did not often think of this type of examination, and he stressed the point that unless it is borne in mind the study may not be requested in those cases in which it would be of the greatest value.

In 1947 Fox [6] presented iodized oil studies of chronically distended tear sacs and stressed the importance of roentgen visualization when surgery is contemplated.

The most recent addition to the literature was that of Thompson and Elstrom,[7] in 1949. They recommended the injection of a warmed iodized oil and employed the prone position for the x-ray exposures.

SELECTION OF PATIENTS

Patients for this study, selected from the Washington University eye clinic and from private practice, were limited to those having no history of ocular or lacrimal apparatus disease and no history of otolaryngological disease. In a few patients there was suspected disease of the lacrimal system on one side, and in these instances the uninvolved side was the only one used in this series. No patient in whom bilateral lacrimal duct disease was suspected, or later found on x-ray study, was used.

Thirty patients were examined over the period of the last year. Bilateral study of the lacrimal apparatus was obtained in all. Twenty of the 60 lacrimal tract studies were discarded because of a history of disease of the tear sac or duct, x-ray evidence of previously unsuspected pathology, or faulty technique. This left a total of 40 lacrimal tracts, exhibiting what were considered to be normal dacryocystograms, for use in this study.

Of our 30 patients, 25 were white and 5 were Negroes. Nine were males and 21 were females.

SELECTION OF CONTRAST MEDIA

After testing numerous aqueous and oily contrast media, ethyl iodophenyl undecylate (Pantopaque; Keleket) was selected as the dye best suited for injection.*

* The following contrast media were tested:

Aqueous	Oil-Type
Sodium iodomethamate U. S. P. (Neo-Iopax 50%)	Iodized oil U. S. P. (Lipiodol)
Sodium acetrizoate (Urokon) 70%	Ethyl iodophenylundecylate (Pantopaque)
30% pH 5	
30% pH 7	

Each of the dyes was instilled into the conjunctival sacs of rabbits, and, after this preliminary investigation, the various substances were similarly applied to human subjects. None of the aqueous media produced any side-effects after being instilled into the rabbit eyes. The oils, however, produced a minimal mechanical discomfort, evidenced by rubbing and blinking the eyes.

In the human volunteers, three solutions were used, without conjunctival anesthesia. These were ethyl iodophenylundecylate, sodium acetrizoate 30% (pH 7), and sodium iodomethamate 50%. The ethyl iodophenylundecylate caused a moderate amount of local discomfort, evidenced as burning of a short duration. The sodium acetrizoate 30% caused no local discomfort but was discarded when the subjects complained of a very bitter, lingering taste in their throats. The sodium iodomethamate 50% produced a powdery deposit on the lid margins, moderate burning of the eye, and minimal pericorneal injection. Fluorescein staining revealed no corneal damage from any of these contrast media, and no marked conjunctival irritation was produced.

A similar study is now being conducted using sodium iodomethamate as the contrast medium. This study will offer a comparison between the use of aqueous and oil-type injection solutions.

Pantopaque (Keleket) is a mixture of ethyl esters of isomeric iodophenylundecylic acids marketed as an absorbable, oil-type contrast medium of low viscosity. It was originally developed for myelography. It is put up in a 3 cc. sterile ampoule, a size which is convenient for our purpose.

Some of the factors which influenced this selection may be noted: (*a*) It is easy to inject—it has a lower viscosity than iodized oil and does not require thinning before injection; (*b*) it offers excellent contrast and will demonstrate more accurately small irregularities in the outline of the lacrimal tract than will the more viscous preparations, and, (*c*) it offers freedom from reactions and side-effects.

PROCEDURE

A. Injection Technique.—Acceptance of roentgenography of the lacrimal apparatus by all ophthalmologists depends on establishing a technique which (*a*)

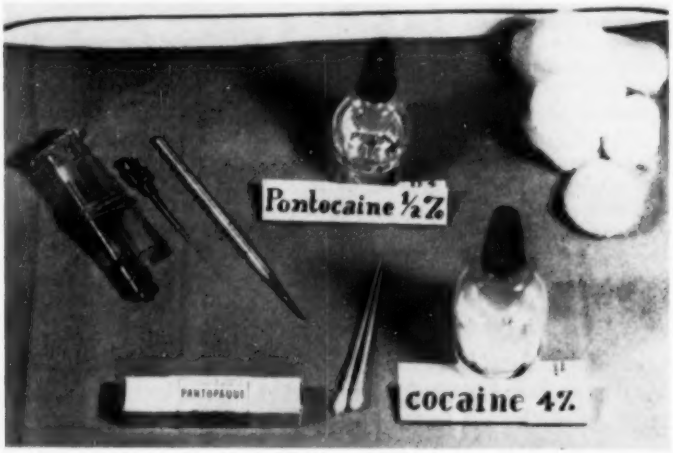

Fig. 1.—Materials required for dacryocystography.

is uncomplicated; (*b*) can be performed rapidly; (*c*) employs materials which are readily available, and (*d*) is painless. After consideration of several methods for filling the lacrimal apparatus with the dye, the technique decided upon was essentially that practiced in most offices for routine irrigation of the lacrimal system. Figure 1 illustrates the minimum equipment required for the procedure.

Anesthesia was effected with topical tetracaine (Pontocaine) hydrochloride, 0.5%, followed by a cocaine (4%)-soaked cotton applicator placed between the closed lids at the puncta. The patient was seated at the sinus x-ray machine, before the upright cassette holder, and positioned for the first exposure. The lower punctum was dilated; a gold lacrimal needle on a 2 cc. Luer-Lok syringe was inserted into the lower canaliculus as far as the nasal wall of the sac, withdrawn slightly and 1 cc. of the dye injected under gentle, even pressure. The head was again placed in position, and the posteroanterior picture was taken for the first eye. As rapidly as the cassette could be changed, a lateral view was taken for this eye.

An identical routine was then followed on the fellow eye, except that an oblique film was taken, rather than a lateral.

Few complications were encountered using this technique.† There was no allergic reaction or local irritation associated with the ethyl iodophenyl undecylate (Pantopaque). The patients generally experienced no pain or discomfort. They were cautioned to expect some oil in the throat and were advised that it was harmless.

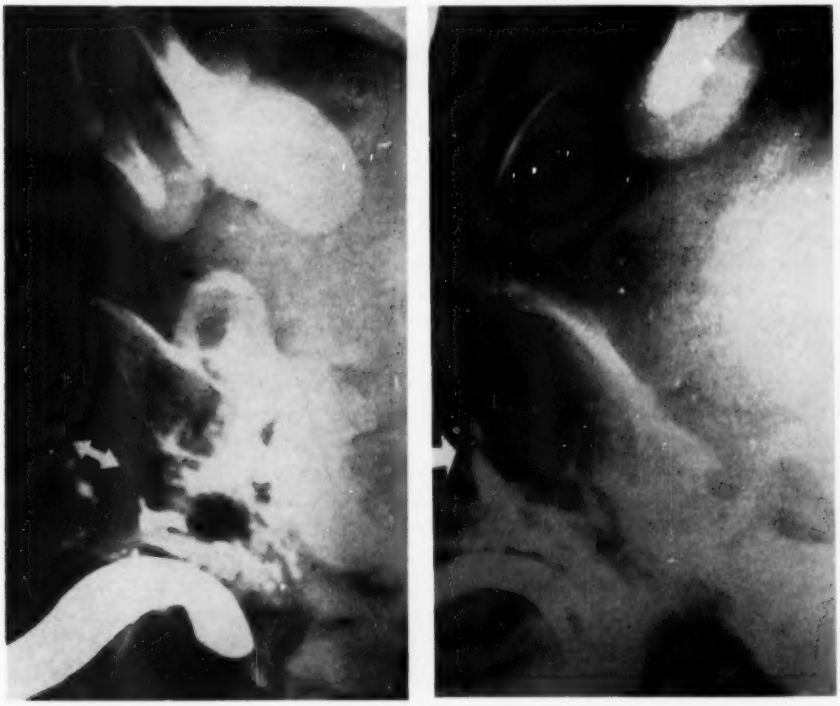

Fig. 2.—Left, simultaneous visualization of the two nasolacrimal ducts in the oblique view. Right, superimposition of the two shadows in the lateral view of the same patient.

B. Roentgenographic Technique.—After experimenting with chin-nose and forehead-nose (Caldwell) posteroanterior exposures, and with oblique and lateral views, the following routine was selected:

1. Forehead-nose (P.A) exposure of the first eye.
2. Lateral exposure of the first eye
3. Forehead-nose (P.A.) exposure of the second eye
4. Oblique exposure of the second eye
5. Posteroanterior exposure of both eyes at 30 minutes, as a follow-up film.

The Caldwell and lateral views were easiest for the ophthalmologist to interpret and simplest to orient with regard to anatomic landmarks.

† In one patient, the canaliculus was damaged during the introduction of the lacrimal needle and the dye extravasated into the lower lid. Over the ensuing three or four weeks, the dye settled, formed an elliptical mass at the inferior orbital margin, and slowly disappeared.

The oblique view presented a roentgenographic shadow closely resembling the lateral view but more difficult to orient anatomically. When only one lacrimal system was to be studied, posteroanterior and lateral films were chosen. When a bilateral study was undertaken, the oblique replaced the lateral view for the second eye, because the superimposition of this shadow on the previously injected tract obscured the detail. This is illustrated by Figure 2, showing the two distinct lacrimal shadows in the oblique view, but almost exact superimposition of the two shadows in the lateral view.

The use of a single injection made necessary the development of a procedure using a minimum of time between the injection of the dye and the taking of the

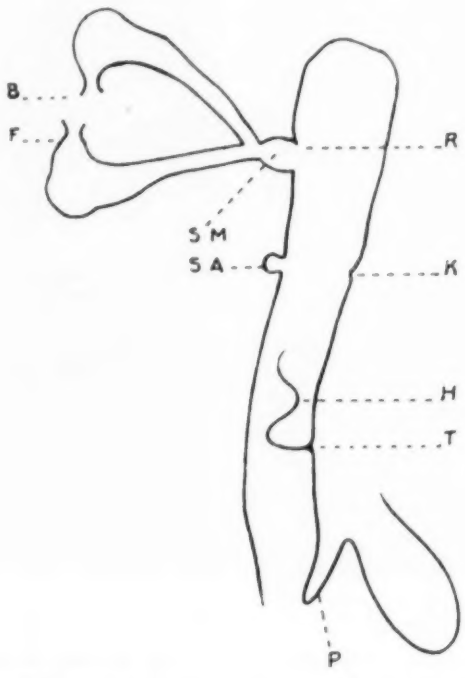

Fig. 3.—Anatomy of the normal nasolacrimal passages (Duke-Elder). *B*, valve of Bochdalek; *F*, valve of Foltz; S. M., sinus of Maier; *R*, valve of Rosenmüller; *S.A.*, sinus of Arlt; *K*, valve of Krause; *H*, spiral valve of Hyrtl; *T*, valve of Taillefer; *P*, plica lacrimalis, or valve of Hasner.

picture. By positioning the patient upright at the cassette holder before injection, the first film was taken within 5 to 10 seconds after withdrawing the lacrimal needle, and the second film 20 to 30 seconds later. The latter included changing the cassette and cocking the Bucky diaphragm. The sitting position was chosen because it shortened the procedure and because it did not interfere with the normal influence of gravity on the drainage of the lacrimal tract.

It became evident, early in this study, that much information was to be derived by using the follow-up film to observe the behavior of the dye in the lacrimal system.

This follow-up film best provided information concerning the normal function of the system, as well as the location of block in an abnormal tract. Complete filling of the nasolacrimal tract was not found necessary for conclusions regarding the presence of pathologic changes or of abnormal function.

RESULTS

This series of controlled studies, setting forth the essentials of the normal dacryocystogram, is the outgrowth of 10 years of a more or less haphazard use of the diagnostic method. Consequently, the results of the present study revealed two basic trends, neither of which was particularly surprising.

First, we found a rather wide variation in "normal" lacrimal tracts, due to differences in anatomy, in degree of filling of the system, and in roentgenographic technique. Second, despite these variations, inherent in all contrast roentgenographic methods, there emerged a fairly consistent normal pattern, from which it was possible (1) to obtain an impression (for ethyl iodophenylundecylate) of the normal picture of each portion of the lacrimal drainage apparatus; (2) to construct therefrom a "composite" normal, usable as a point of departure for clinical study of pathology of the tract, and (3) to establish criteria for the interpretation and evaluation of these x-rays.

Anatomy.—In the normal lacrimal system (Fig. 3) the sac lies flattened in the bony lacrimal fossa, its lumen a shallow cleft, 4-8 mm. wide in its anteroposterior diameter and 1-2 mm. in lateral diameter. The canaliculi empty into the sac through a digitation at its temporal side (the sinus of Maier), at the junction of the upper third and the lower two-thirds. The sac is continuous with the membranous nasolacrimal duct, which is sinuous or irregular in course, studded with "valves," or constrictions, at variable levels and in varying numbers. It is about 25 mm. long; it makes a short arc terminally to empty into the nose in the lateral wall of the inferior meatus. The duct widens out from a cleft into an irregular, flattened "tube." The sac is generally considered to be that portion of the membranous tube which lies within the orbit; sometimes, a small "sinus" of Arlt, on the temporal side, marks the separation of sac and duct.[8]

As will be brought out, the normal dacrycystogram demonstrates rather well the essentials of anatomy described above. No characteristic differences were noted between the sexes; the few small children examined provided no clue as to significant differences between adults and children. Since only one-fourth of the patients examined were Negroes, no conclusions as to racial differences could be drawn.

Roentgenographic Detail.—(*a*) Lids, canaliculi: Visualization of the lid margins and cilia was found to be most helpful in orienting the position of the sac and its relation to the lower portions of the tract. It was aided by wiping any excess of ethyl iodophenylundecylate gently over the closed lids immediately after completing instillation of the oil. The appearance of the oil, lying in beaded fashion along the cilia, is shown in Figure 4.

In the normal tract, the canaliculi are not ordinarily visualized. Where there is a high obstruction in the system (at or above the sac-duct junction), or partial obliteration of the sac, the resistance to injection of the dye may be sufficient to produce filling of the canaliculi, as shown in Figure 5.

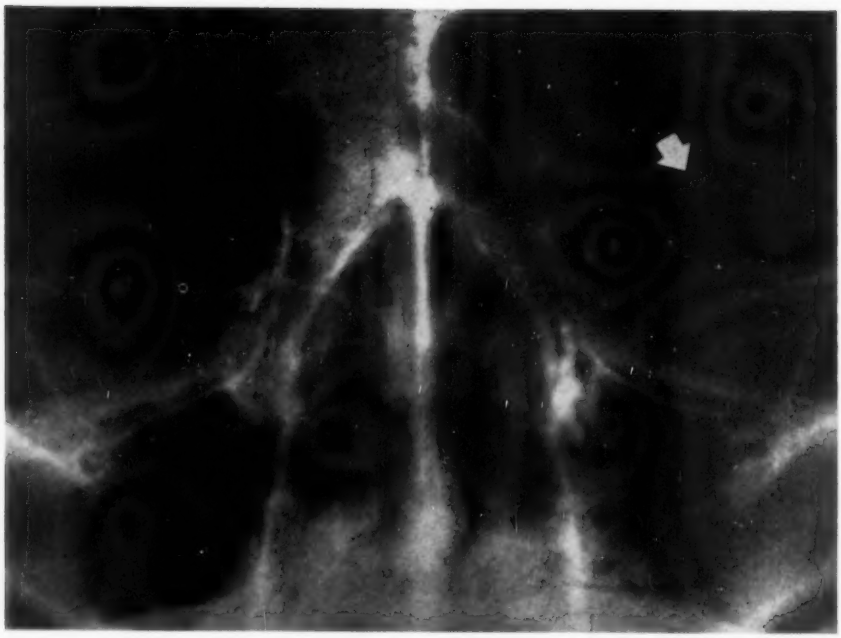

Fig. 4.—Visualization of the lid margins of both eyes and localization of the nasal canthus by means of beaded dye along the cilia. The arrow shows the upper lid margin of the left eye.

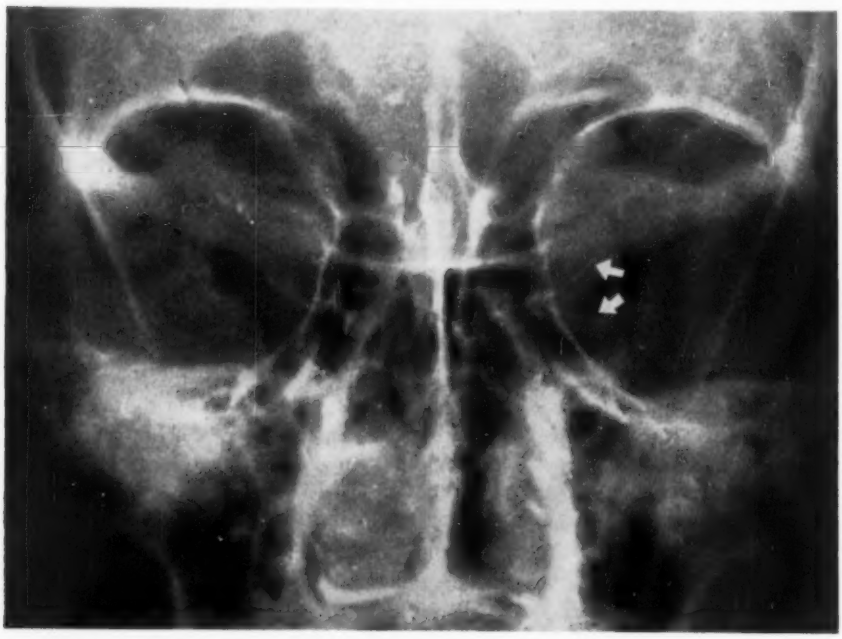

Fig. 5.—Visualization of both left canaliculi in a patient with obstruction of the left lacrimal passages and a shrunken lacrimal sac.

Fig. 6.—Normal posteroanterior view of the left lacrimal sac, showing the gently curving outline and the widening in the lower portion.

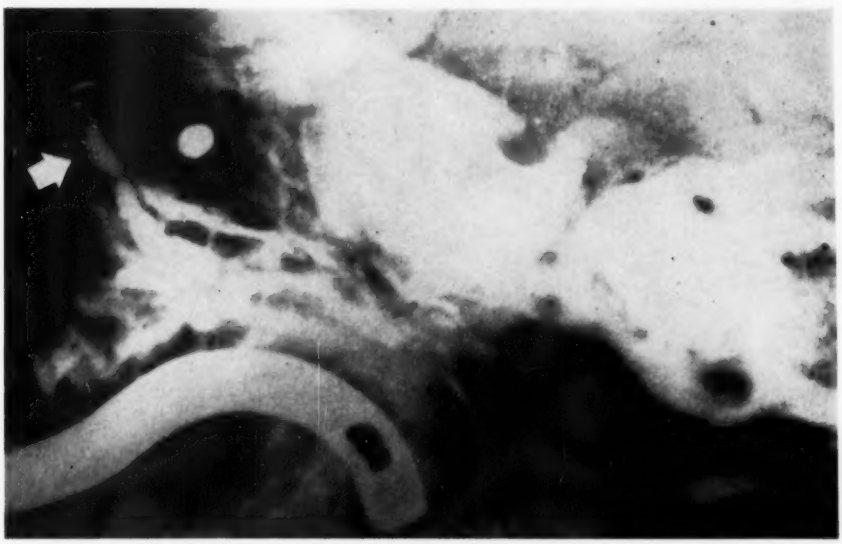

Fig. 7.—Lateral view of normal sac (in child), showing the broader lateral shadow and a shallow constriction at the sac-duct junction.

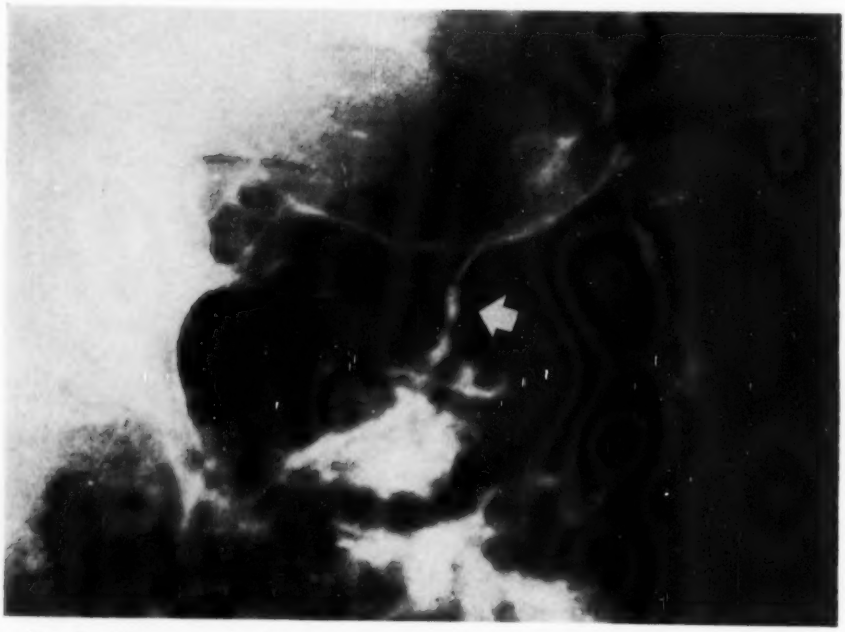

Fig. 8.—Oblique visualization of the normal sac and duct. The arrow points to the upper half of the duct.

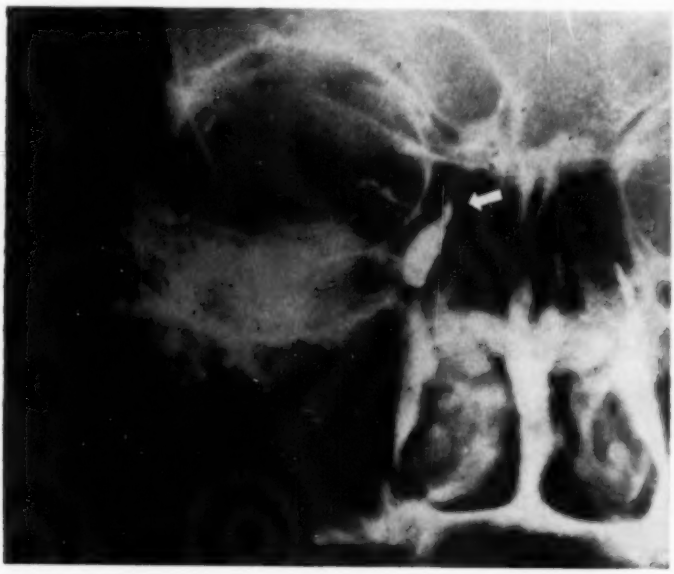

Fig. 9.—Filling of the cupola in a distended sac, with obstruction below. Arrow is directed toward cupola.

Fig. 10.—Right lacrimal passages, showing notching at the sac-duct junction.

Fig. 11.—Normal posteroanterior view of both ducts, showing widening of the shadow in the upper third, and in the lower third near the ostium. The two arrows are directed toward the lower portions of the sacs.

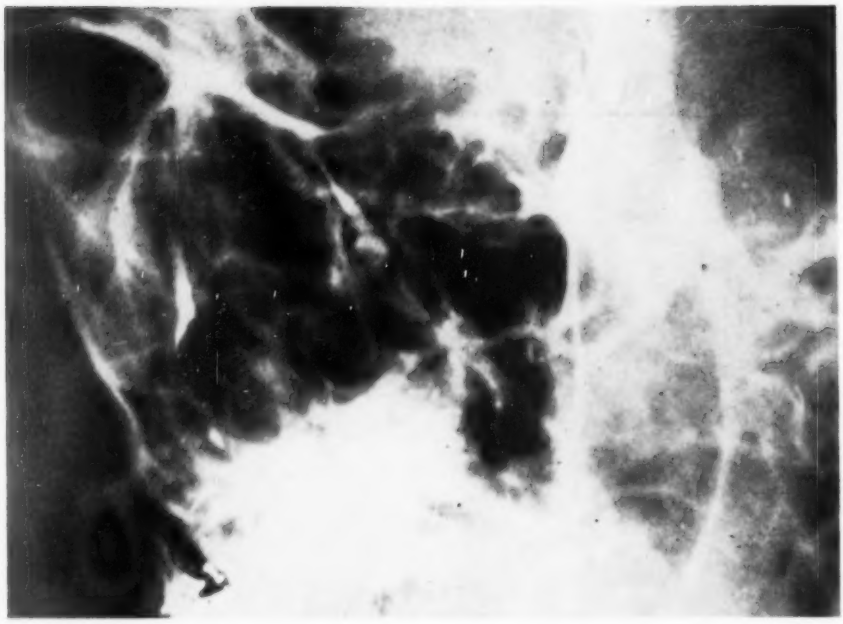

Fig. 12.—Oblique view of normal ducts; the right duct shows spiral configuration.

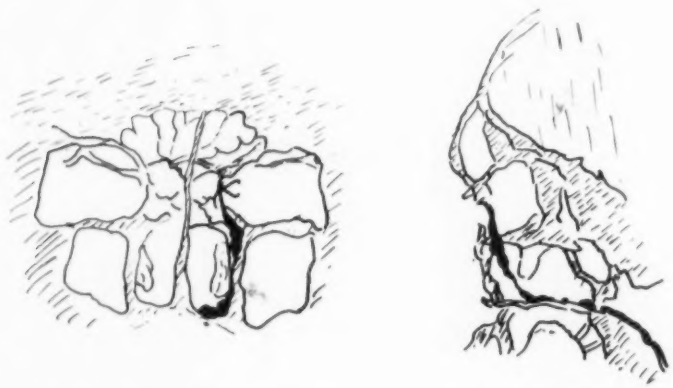

Fig. 13.—Composite drawing of the roentgenographic visualization of the lacrimal drainage system; posteroanterior and lateral views.

(*b*) Lacrimal Sac: The forehead-nose (Caldwell) views show the normal sac as a thin ribbon, 1 to 2 mm. wide, broadening gradually in the lower third (Fig. 6). It has a gentle curvature, with the concavity temporal, producing a "scimitar" shape.

In the oblique and lateral views, the sac is visualized as a wider opaque band (2 to 4 mm.), without a characteristic outline, but generally being rather straight or exhibiting shallow undulations (Figs. 7 and 8). It was significant that the cupola of the sac (above the canaliculi) did not normally fill with dye. Only when obstruction was present could this portion of the sac be visualized (Fig. 9).

(*c*) Nasolacrimal Duct: In the posteroanterior position, which gives the most consistent findings, there was frequently noted a shallow constriction at the lower end of the sac (Fig. 10). This was interpreted to lie at the upper edge of the osseous portion of the nasolacrimal duct. The duct invariably filled well in its upper third, whereas in the midportion the pattern was less uniform and the dye was generally sparse or absent. Then, at the lower end of the duct, a greater accumulation of dye was again found, in a "hockey-stick" curvature, emptying into the nasopharynx below the inferior turbinate, where the dye often puddled (Fig. 11).

The pattern of visualization in the ducts did not provide any clue to the position or uniformity of the membranous "valves," or folds. In the upper half of the duct, consistently well visualized, the irregularities or valves were not constant. Many of the films showed a sinuous, or frankly tortuous, band. Some were concha-like in appearance, as shown in Figure 12. The lateral and oblique views of the upper half of the duct added little characteristic detail, although they demonstrated a wider duct shadow on the x-ray. It should be noted that these views did not, as a rule, enable one to make a sharp identification of the sac-duct junction or of the nasal ostium.

(*d*) Nasopharynx: The appearance of dye in the floor of the nose or in the nasopharynx was indicative of mechanical patency of the lacrimal system, and was invariably present on the very first film in the normal patient. Accumulations of the dye are clearly visible in the floor of the nose, in Figure 11, and in the pharynx, in Figure 7.

The "Composite" Normal Dacryocystogram.—Although all the characteristics described above were not present in every case, it was possible, from our observations and from photographs, such as those presented in the preceding paragraphs, to reconstruct the composite figure shown in Figure 13. It can be seen that the nasolacrimal tract, as visualized roentgenographically, is quite consistent with the description of the normal anatomy outlined previously.

INTERPRETATION AND EVALUATION OF FINDINGS

From the films employed in this study, one can formulate conclusions regarding (1) the roentgenographic apearance of the elements of the lacrimal apparatus; (2) the patency of the system, and (3) the state of functioning of the system as a drainage mechanism.

1. *Appearance.*—The roentgenographic appearance of the typical lacrimal system has been described. Because of the relatively low viscosity of the ethyl iodophenylundecylate, some sacs filled very little, or not at all, and poor filling was therefore not considered abnormal. Indications of abnormality of the sac were (*a*)

distension of the sac beyond the limits indicated in the description; (*b*) an elliptical or oval sac outline (Fig. 9), or (*c*) filling of the cupola, especially if the canaliculi are visualized, and (*d*) retention of the dye in the sac.

Distention of the upper part of the duct, on the other hand, was not considered abnormal in the absence of an enlarged sac. The duct was considered normal if the system was patent and if there was no retention of dye on the follow-up films.

In this connection, it should be mentioned that the radiologists, in interpreting these films, have avoided the words "normal sac or duct," and "distension," and do not use the terms "complete" or "incomplete filling" of the system, since the technique used would not result in complete filling unless there were an obstruc-

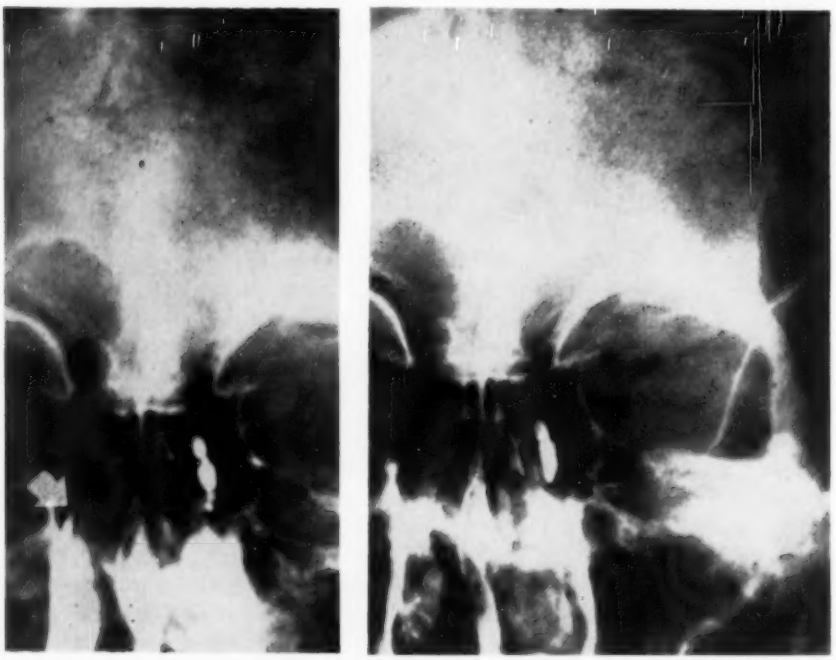

Fig. 14.—Left, immediately after injection, visualization of dye in the right nasolacrimal system, with distension of the left lacrimal sac. Right, complete emptying of the right side after 30 minutes. The left side remains relatively unchanged.

tion. The findings are described in terms of "visualization" or "nonvisualization," "patency," or presence of "residual," indicating partial or complete obstruction.

2. *Patency.*—One of the significant conclusions which can be drawn from these x-rays is the determination of whether the drainage system is patent. Although patency can usually be determined by office irrigation of the system, the roentgenogram proves it without equivocation. It is especially helpful with children and with uncooperative patients.

In this series, every normal system exhibited dye in the nasopharynx. In the posteroanterior film, this was best seen beneath the inferior turbinate. In the lateral views, globules of the dye were distributed along the floor of the nose, over the soft

palate, and in the hypopharynx. In a nonpatent system, no dye appeared in the nasopharynx, and the level of obstruction could be determined by noting the lowest level where the dye settled.

3. *Residual.*—The most valuable information which can be gained by the dacryocystogram is the evaluation of the drainage function of the lacrimal system. Only by x-raying the tract in this manner is it possible to determine whether or not the sac and duct empty properly. The determination of function depends upon the presence or absence of residual dye, seen on the follow-up film, and to some extent on the amount and position of this dye. Figure 14 shows on the right side a partially empty normal sac and a normal duct, and on the left side a distended pathological sac with no visualization of dye in the duct. In the follow-up film, at 30 minutes, the right side is entirely empty, while there has been no evidence of emptying of the accumulated dye in the left sac.

In order to determine the emptying time of the normal lacrimal system, follow-up films were taken at 15, 30, 45, or 60 minutes after injection of the dye. As may be noted in the accompanying Table, the time required for the nonpathologic tear

Amount of Residual Dye in Follow-up Films

Time of Follow-Up Picture, Min.	No. of Eyes	Sac				Duct			
		No Change in Dye	Partly Empty	Trace of Dye	No Dye	No Change in Dye	Partly Empty	Trace of Dye	No Dye
15	19	2	9	1	7	3	13	3	0
30	9	0	0	0	9	0	0	4	5
45	11	0	0	3	8	0	0	7	4
60	3	0	0	0	3	0	0	0	3

sac to become completely or almost completely empty is 30 minutes or less. Many (11 of 19) normally functioning systems revealed almost no disappearance of the dye from the sac after 15 minutes. All (nine of nine) of those examined at 30 minutes were completely empty.

A study of the emptying time for the duct revealed that none of the normal lacrimal ducts were empty completely in 15 minutes, and 16 of the 19 revealed total or subtotal filling. In 30 minutes, all the ducts viewed were empty or showed but a trace of dye. From these observations it was concluded that the normal emptying time for the lacrimal sac and duct (for ethyl iodophenylundecylate) is between 15 and 30 minutes and that the follow-up film should be taken at 30 minutes. A significant retention of dye in the sac or duct after this time indicates a functional obstruction in the system, even though the usual aqueous irrigating solutions may pass through freely.

4. *Is Bilateral Injection Necessary?*—It may be seen from the preceding discussion that the usual pattern of the lacrimal tract is consistent enough to warrant the study of the pathologic side alone, routinely. However, in the case of a patient who complains of unilateral tearing, and in whom the system has been found patent by office irrigation, a comparison of the follow-up films for both sides may demonstrate impaired drainage on the involved side.

When there is an obstruction, and the system cannot be irrigated freely, a unilateral film is sufficient to locate the level of the block.

REPORTING THE DACRYOCYSTOGRAM

Interpretation of the x-rays of the lacrimal tract depends upon three basic observations: the contours and filling of the system; the patency (shown by dye in the nasopharynx), and the function, or "mechanical" status, indicated by the amount and position of the dye in the follow-up film. These observations may be reported concisely, together with the clinical impression, on a card such as that illustrated in the accompanying form.

Little purpose is served by a wordy description of the appearance of the dye in the system. However, the oculist who studies the films personally will rapidly become adept at forming a useful clinical impression upon which to base his therapeutic program.

Name..... Date.....

X-ray No..... Age.....

Referred by..... W C M F

History:

Findings:	*Right*	*Left*
P.A.		
Lat. or obl.		
Nasopharynx		
30" follow-up		

Remarks:

Impression:

.....M.D.

Form for Reporting the Dacrycystogram

SUMMARY AND CONCLUSIONS

A simple technique for dacryocystography is presented, using ethyl iodopheyl-undecylate (Pantopaque) as the contrast medium.

From a study of 30 patients, details of the normal dacryocystogram were elicited.

The forehead-nose (Caldwell) and lateral projections were used to visualize the nasolacrimal tract. In bilateral studies, an oblique view was substituted for the lateral of the second eye.

Bilateral study is desirable for evaluation and comparison of the function of the two drainage systems.

The pattern of dye in the drainage system, as indicated by a composite diagram of the normal x-rays, follows closely the usual descriptions of the gross anatomy of these structures.

Complete filling of the drainage system is not necessary. The emptying time, demonstrated in a 30-in. follow-up film, provides the most valuable information regarding the function of the system. Residuals of more than traces of the dye, in the follow-up film, are indicative of abnormal drainage function.

Personal inspection of the x-rays by the ophthalmologist is valuable in forming a clinical impression as a basis for treatment.

The Pantopaque was supplied by Lafayette Pharmacal, Inc., Lafayette, Ind.

REFERENCES

1. Ewing, A. E.: Roentgen Ray Demonstrations of the Lacrimal Abscess Cavity, Am. J. Ophth. **24**:1-4, 1909.

2. von Szily, A.: Pathology of the Tear Passages as Revealed by X-Ray, Klin. Monatsbl. Augenh. **64**:31-44, 1920.

3. Campbell, D. M.; Carter, J. M., and Doub, H. P.: Roentgen Ray Studies of the Naso-lacrimal Passageways, Arch. Ophth. **51**:462-470, 1922.

4. Hourn, G. E.: X-Ray Visualization of the Naso-Lacrimal Duct, Ann. Otol. Rhin. & Laryng. **46**:962-975, 1937.

5. Spackman, E. W.: X-Ray Studies of the Nasolacrimal Duct, Am. J. Ophth. **21**:518-524, 1938.

6. Fox, S. A.: Lipiodol Studies of Chronic Dacryocystitis, Am. J. Ophth. **30**:878-884, 1947.

7. Thompson, J., and Elstrom, R. T.: Radiography of the Nasolacrimal Passageways, M. Radiog. & Photog. **25**:66-69, 1949.

8. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. I, St. Louis, C. V. Mosby Company, 1940, p. 238.

BACTERIOLOGY OF THE EYE

I. Normal Flora

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THE BACTERIA which may be recovered from the normal human eye have been recorded in the literature a number of times.* The consistent findings of Micrococcus pyogenes var. albus (Staphylococcus albus) and diphtheroids in the great majority of cultures from the conjunctivae and lids of normal eyes characterize these reports. The present investigation is a study of the organisms grown from eye cultures of patients admitted to the Thigpen-Cater Eye Hospital for cataract extraction over the period from 1947 to 1952. The organisms recovered are considered as normal flora in that there are included only those cultures from patients who, upon ophthalmological examination at the time cultures were made, revealed no evidence of an infectious process in either eye. A point of interest which warrants a brief report of the results was the frequency with which certain members of the enteric Gram-negative group of bacteria were encountered. The importance of these organisms as etiologic agents of infection following cataract extraction will be considered in another article.[7]

METHODS AND MATERIALS

Patients were admitted to the hospital 48 hours prior to the operation for cataract extraction. Examination of the eyes was made on admission by physicians in the department of ophthalmology, and cultures of the lid margin and conjunctiva of both eyes were made by the examiner. For lid culture, a sterile cotton swab moistened in nutrient broth was rubbed over the outer lid margin, then streaked over a quarter-section of both a blood agar and a milk agar plate. The plates were previously divided into four sections by marking on the bottom of each plate with a wax pencil, indicating each quarter with the letters RL, RC, LL, and LC for cultures from the right lid and conjunctiva and the left lid and conjunctiva, respectively. Material for conjunctival culture was obtained by rubbing a sterile, broth-moistened swab over the lower conjunctiva, then streaking as above on the appropriately marked area of each culture medium. Thus, each plate was inoculated with material from the lid and conjunctiva of both the right and the left eye. The milk agar plate was used to facilitate the identification of M. pyogenes var. aureus (Staph. aureus), should it be present, by the enhancement of pigment production. Cultures incubated aerobically at 37 C. for 24 to 48 hours were examined and the organisms grown were identified.

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* References 1, 2, 3, 4, 5, and 6.

RESULTS AND COMMENT

The organisms encountered and their frequency in cultures from the lids and conjunctivae of both eyes of 1,604 patients are listed in the Table. Figures from studies by Khorazo and Thompson [4] are also listed for comparison. Their series was the only one discovered in which the total number of Gram-negative rods recovered in cultures from normal eyes was greater than a small fraction of 1%.

Axenfeld,[1] in 1908, wrote that white staphylococci and diphtheroids could be found regularly on the normal conjunctiva. His statement, "No other findings are constant," has been borne out time and again, but his observation of the Pneumococcus as the commonest of the pyogenic organisms found has not been consistently

Organisms Encountered and Their Incidence in Preoperative Eye Cultures

Organism	Conjunctivae		Lids		Khorazo and Thompson, 1935 [4]
	No.	%	No.	%	% *
M. pyogenes var. albus	1,097	68	1,531	95	41
M. pyogenes var. aureus	105	7	199	12	23
M. citreus	7	< 1	15	< 1	..
Diphtheroids	531	33	612	40	36
Sarcina	19	1	58	3	1
Streptococcus pyogenes	4	< 1	2	< 1	1.2
Viridans type of streptococci	7	< 1	4	< 1	3.4
Indifferent streptococci	2	< 1	3	< 1	..
Pneumococci	8	< 1	7	< 1	2.6
Neisseria catarrhalis	3	< 1	10	< 1	..
N. sicca	3	< 1	4	< 1	..
B. subtilis	5	< 1	26	2	(9)
A. aerogenes	21	1	25	2	(1)
P. vulgaris	19	1	24	1	(6)
Ps. aeruginosa	8	< 1	11	< 1	(4)
Esch. coli	3	< 1	3	< 1	(5)
A. faecalis	1	< 1	3	< 1	(3)
K. pneumoniae	0	..	3	< 1	..
Unidentified Gram-negative rods	23	1	38	2	..
Monilia (Candida)	2	< 1	3	< 1	(5)
Cryptococcus	1	< 1	0	..	(5)
No growth	374	23	45	3	17
No. of patients	1,604	..	1,604	..	1,122

* Numbers in parentheses indicate actual numbers, not percentages.

confirmed. Instead, M. pyogenes var. aureus has been relatively the most frequent organism of the pyogenic group cultured from normal eyes in this, as well as other, series.

At the outset of these studies colonies of both M. pyogenes var. albus and M. pyogenes var. aureus that were isolated were tested for their ability to coagulate human plasma. Both hemolytic and nonhemolytic isolants of M. pyogenes var. aureus were occasionally coagulase-positive, while those identified as M. pyogenes var. albus were consistently coagulase-negative. Coagulase testing was discontinued after several months.

Axenfeld also stated, in regard to the normal conjunctiva, "It is only to be expected that all those organisms can be found in it which occur in air, in washing water, in the skin around, or on anything with which the eye may come in contact." The skin would appear to be the commonest source of organisms which may be found on the conjunctiva, and the rather wide variety of bacteria recovered from

these cultures all may, at times, be found on the skin. In only a very few instances were colonies of Bacillus subtilis found on culture plates in such numbers as to suggest that this organism was actually growing on the lids or conjunctivae. Usually only a single colony or two was found on the culture medium when this aerobic spore formerly was grown, and only those colonies which grew along the inoculation streaks were considered in recording B. subtilis as part of the normal flora. The same was true in the case of organisms belonging to the genus Sarcina, although there were many more instances in which numerous colonies were found.

The frequency with which certain Gram-negative bacilli were encountered is greater than heretofore recorded. These organisms, members of the enteric Gram-negative rods, were cultured from the conjunctivae of 5% of the patients and from the lids of 7%. Their presence in the eyes of patients who undergo cataract extraction can be of concern to the ophthalmologist in calculating the risk of operative infection. At the present time it is the practice of the staff of the ophthalmology department of the Medical College of Alabama to postpone cataract extraction if Gram-negative rods are cultured from the lids or conjunctiva of either eye of patients scheduled for surgery. This routine postponement has developed as a result of the unfortunate occurrence of postoperative panophthalmitis in several patients from whom Gram-negative rods were grown in preoperative cultures of the lids and conjunctivae.

In the normal flora studies reported by Khorazo and Thompson [4] these Gram-negative bacilli were recovered in only 19, or 1.6%, of conjunctival cultures from 1,122 patients. They encountered Aerobacter aerogenes only once, while it was the most frequently grown member of the group met with in the present study. It is not unlikely that it occurred with greater frequency than indicated in the Table, because some of the organisms listed as "unidentified Gram-negative rods" presumably were A. aerogenes. In the "unidentified" group are those Gram-negative rods which were not specifically identified by biochemical reactions or other procedures. Colonies of these bacilli were not always identified immediately after isolation, but pure cultures of such organisms were stored in the refrigerator for identification later. A considerable number of these cultures were prematurely discarded by an enthusiastic laboratory maid and therefore must be listed as "unidentified." With the exception of one isolation, in which the colonies had an orange pigment, these "unidentified Gram-negative rods" produced rather large gray or cream-colored colonies on the original blood agar and milk agar medium. On the basis of the common observation of "swarming" growth typical of Proteus vulgaris, as well as the striking hemolysis and frequent evidence of pigment production by Pseudomonas aeruginosa in almost every isolation of this organism, it would not be unreasonable to presume that A. aerogenes, Escherichia coli, and perhaps Alcaligenes faecalis were predominant in the "unidentified" group. On several occasions an organism tentatively identified as A. faecalis would, upon further study, be found to belong to the genus Pseudomonas. The three isolations of Klebsiella pneumoniae (Friedländer's bacillus) are questionable in their identification, inasmuch as they were not confirmed by type-specific serological reactions and could have been mucoid organisms belonging to Aerobacter rather than Klebsiella.

SUMMARY AND CONCLUSIONS

The bacterial flora of the eyes of 1,604 patients is reported. M. pyogenes var. albus and diphtheroids were recovered in culture more frequently than any other organisms.

Certain Gram-negative enteric bacilli occurred with greater frequency than heretofore reported.

Dr. Alston Callahan, Professor of Ophthalmology, Medical College of Alabama, and members of his staff assisted in this study

REFERENCES

1. Axenfeld, T.: The Bacteriology of the Eye, translated by Angus McNab, London, J. B. Baillière, Tindall & Cox, 1908.

2. Lucic, H.: Bacteriology of the Normal Conjunctival Sac, Am. J. Ophth. **10**:829, 1927.

3. Keilty, R. A.: The Bacterial Flora of the Normal Conjunctiva with Comparative Nasal Culture Study, Am. J. Ophth. **13**:876, 1930.

4. Khorazo, D., and Thompson, R.: Bacterial Flora of the Normal Conjunctiva, Arch. Ophth. **18**:1114, 1935.

5. Weiss, C., and Shevky, M. C.: Clinical Bacteriology and Cytology of Some Ocular Infections, Am. J. Clin. Path. **14**:567, 1944.

6. Rodin, F. H.: Bacteriologic Study of Human Conjunctival Flora, Am. J. Ophth. **28**:306, 1945.

7. Winkler, C. H., Jr., and Cason, L.: Bacteriology of the Eye: II. The Role of Gram-Negative Bacilli in Infections Following Cataract Extraction, A. M. A. Arch. Ophth., this issue, p. 200.

BACTERIOLOGY OF THE EYE

II. Role of Gram-Negative Bacilli in Infections Following Cataract Extraction

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THE DEPARTMENT of Ophthalmology in the Medical College of Alabama in 1947 established the practice of routine preoperative cultures from the lids and conjunctivae of the eyes of patients admitted to the Thigpen-Cater Eye Hospital for cataract extraction. This afforded an opportunity to learn something about the bacterial flora of the normal eye, and because infection occurred in a few cases after cataract extraction, there was also an opportunity to study the etiologic agents of such infection.

The preoperative culture findings, considered as normal flora of the eye, have been reported elsewhere.[1] This paper is a report of the bacteria recovered from 11 patients with postoperative infections in a series of 1,653 cataract extractions. An attempt has been made to relate the origin of infection to the preoperative bacterial floral or to an exogenous source of infection.

MATERIALS AND METHODS

The technique used in preoperative culture of the lids and conjunctiva of both eyes of patients to be operated upon for cataract extraction has previously been described.[1] When postoperative infection was first noted, culture of the exudate from the infected eye was made by streaking blood agar and milk agar plates. At the same time a smear of the exudate was made on a slide for Gram staining and microscopic examination. Cultures were incubated aerobically at 37 C. for 18 to 24 hours. Growth was always apparent by this time, and isolated colonies were picked and identified. Antibiotic- and sulfonamide-sensitivity tests were performed on the Gram-negative bacilli grown in culture, but the results of such tests will not be considered in this report.

RESULTS AND COMMENT

The preoperative and postoperative culture findings from those patients in which panophthalmitis developed after cataract extraction are listed in the Table. Cataract extraction was extracapsular in Patients 1 and 6 and intracapsular in the remainder.

At the beginning of this series the presence of Gram-negative bacilli in preoperative cultures was not considered to be a contraindication to cataract extraction. A survey of the literature on postoperative infection indicated that Micrococcus pyogenes var. aureus (Staphylococcus aureus) was by far the commonest agent of such infection. Organisms which were deemed potential pathogens were strepto-

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cocci, pneumococci, and M. pyogenes var. aureus. When these were encountered in cultures from the lids or conjunctiva of the eye to be operated upon, surgery was postponed until subsequent cultures, after antibiotic therapy, failed to grow any of these bacteria.

The role of Gram-negative bacilli as "opportunists" in causing infection was suspected after the first case of panophthalmitis. Subsequent infections confirmed the potential pathogenicity of members of the enteric group of bacilli, and operation was routinely postponed when such organisms were grown in preoperative cultures from either eye of the patient.

Infection in Patients 1, 6, 10, and 11 was considered to be endogenous inasmuch as the etiology of the infection could be related to preoperative culture findings. Cultures before surgery from Patient 1 revealed the presence of Gram-negative rods, but the plates were discarded without identifying these bacilli. Postoperative infection, from which Aerobacter aerogenes was grown in pure culture, was appar-

Preoperative and Postoperative Culture Findings in Patients with Infection Following Cataract Extraction

Patient	Preoperative Culture *	Postoperative Culture
1	Unidentified Gram-negative bacilli	A. aerogenes
2	P. vulgaris, RL and LL †	M. pyogenes var. aureus
3	No colonies of Gram-negative bacilli	A. aerogenes
4	M. pyogenes var. aureus, RL No colonies of Gram-negative bacilli	A. aerogenes
5	No colonies of Gram-negative bacilli	A. aerogenes and Ps. aeruginosa
6	Unidentified Gram-negative bacilli, RL	A. aerogenes
7	No colonies of Gram-negative bacilli	Ps. aeruginosa
8	No colonies of Gram-negative bacilli	Ps. aeruginosa
9	No colonies of Gram-negative bacilli	Ps. aeruginosa and A. aerogenes
10	Ps. aeruginosa, LL, LC †	Ps. aeruginosa
11	P. vulgaris, RC; M. pyogenes var. aureus, RL	P. vulgaris

* M. pyogenes var. albus or diphtheroids or both were grown in cultures of the lids or conjunctivae from all 11 patients.
† RL, RC, LL, and LC indicate right lid, right conjunctiva, left lid, left conjunctiva, respectively.

ently endogenous. A similar sequence of events occurred in the case of Patients 6, 10, and 11, with the preoperative culture findings and identification of Gram-negative rods correlating with the organisms isolated when infection followed cataract extraction.

From Patient 6, Gram-negative bacilli were grown in preoperative cultures of the right lid, but since the left eye was to be operated upon, their presence was not considered at that time to be a hazard. After infection in this patient the ophthalmology staff postponed cataract extraction when enteric Gram-negative bacilli were encountered in preoperative cultures of either eye. A member of the resident staff misunderstood this routine postponement and proceeded with the operation on the right eye of Patient 10 after Gram-negative rods had been reported from the cultures of the lid and conjunctiva of the left eye.

In the last case (Patient 11) a single colony of Proteus vulgaris from the right conjunctiva was not noticed at the time preoperative culture findings were reported to the ophthalmology staff, but was observed after the bacteriology laboratory was informed that infection had occurred after surgery on the left eye. When Proteus was found in cultures, the organisms usually "swarmed" to form a thin film of

growth over the entire plate in 24 hours, and the distinctive nitrogenous odor suggesting their presence was encountered when the Petri dish culture was opened. Two colonies of hemolytic M. pyogenes var. aureus were grown in preoperative culture of the right lid of Patient 11, but since these were not from the eye to be operated upon and were in such small numbers, their presence was not considered a definite risk at the time of surgery.

The origin of infection in Patients 2 and 3 was not apparent. The preoperative cultures from Patient 2 revealed M. pyogenes var. albus and P. vulgaris, but since the potential pathogenicity of members of the enteric group of bacilli was not clear at this stage, cataract extraction was performed as scheduled. Evidence of infection did not appear until the fifth day after the operation, and in this case a pure culture of M. pyogenes var. aureus was grown from the exudate. This infection was presumed to be endogenous, even though the causative organism was not found in preoperative culture. Nor was the etiologic agent of the infection which occurred in Patient 3, A. aerogenes, grown in preoperative culture. Other patients who had cataract extractions performed the same day, with the same instruments, supplies, and staff, had an uneventful postoperative recovery.

The origin of infection in Patients 4 and 5 was not determined. These occurred after surgery on the same day. Bacteriological studies on supplies and solutions from the operating room after the infections became apparent were unrevealing in an attempt to establish the origin of infection with A. aerogenes and Pseudomonas aeruginosa in these patients. A similar episode occurred 14 months later in the case of postoperative infection with these same organisms in Patients 7, 8, and 9. All had cataract extractions performed on the same day. A. aerogenes and Ps. aeruginosa were recovered in culture from the remaining supply of cotton pledgets used that day at operation.

Evisceration or enucleation of the orbit was performed in 9 of the 11 patients. Two have only light perception or hand movement vision at 2 ft. (60 cm.) remaining in the involved eye.

Reports of infection following cataract extraction have in the past incriminated M. pyogenes var. aureus as the commonest etiologic agent. While the present series of 1,653 extractions is not unduly large, it is of interest that when infection did occur, M. pyogenes var. aureus was found to be the cause in only one case. Instead, Gram-negative rods belonging to the so-called enteric group of bacilli were involved, with A. aerogenes and Ps. aeruginosa the commonest offenders. P. vulgaris, also a member of this general group, was recovered in one case. Callahan [2] and Leopold [3] have indicated the tragic role of enteric bacilli in postoperative infection. These studies confirm and extend the importance of these organisms in the risk of such surgical procedures. That panophthalmitis can be caused by such bacteria when they gain entry into the vitreous is well known and has been often reported after penetrating wounds of the eye.

Routine preoperative cultures from the lids and conjunctivae of all patients before cataract extraction is not a common practice among ophthalmologists in the United States.[2] Cooper [4] has stated that such cultures are of little value. It is the opinion of our ophthalmological colleagues that in view of the importance of certain Gram-negative bacilli as etiologic agents of infection, such routine cultures have

been of definite value in calculating the risk of infection in surgery for cataract. Over the five-year period covered in these studies, operation was postponed in approximately one-sixth of the patients because of the recovery of organisms considered potentially pathogenic from preoperative cultures. About one-fourth of the postponements resulted from the observation of the presence of enteric Gram-negative bacilli on such cultures.

SUMMARY AND CONCLUSIONS

The bacteriological findings in 11 cases of infection following cataract extraction are reported. Preoperative cultures permitted the correlation of organisms grown from the lids and conjunctivae before operation with the etiologic agents of postoperative infection in four cases. An apparently exogenous source of infection was present in seven cases of panophthalmitis.

Certain Gram-negative rods belonging to the enteric group of bacilli were the causative agents of infection following cataract extraction in 10 of the 11 cases. The organisms recovered in culture were A. aerogenes, Ps. aeruginosa and P. vulgaris, and in one case, M. pyogenes var. aureus. The role of Gram-negative bacilli as "opportunists" in postoperative infection and the value of preoperative cultures in discovering their presence are discussed.

REFERENCES

1. Cason, L., and Winkler, C. H., Jr.: Bacteriology of the Eye: I. Normal Flora, A. M. A. Arch. Ophth., this issue, p. 196.

2. Callahan, A.: Effect of Sulfonamides and Antibiotics on Panophthalmitis Complicating Cataract Extraction, A. M. A. Arch. Ophth. **49**:212, 1953.

3. Leopold, I. H.: Surgery of Ocular Trauma, A. M. A. Arch Ophth. **48**:738, 1952.

4. Cooper, E.: Note on Preoperative Eye Cultures, Am. J. Ophth. **18**:850, 1935.

OCULAR SIGNS OF WERNICKE'S DISEASE

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WERNICKE'S disease is a clinical and pathological entity in which ocular motor signs are the most constant finding. Yet extraordinarily few descriptions of it have been reported in the ophthalmic literature,* and little attempt has been made to analyze the diversity of its ocular manifestations. This is remarkable when one considers that without the eye signs one cannot make a clinical diagnosis of Wernicke's disease. Moreover, a quick and accurate recognition of the condition is not merely of academic interest; it becomes a matter of prime practical importance, since this disease has a serious prognosis unless treated specifically and promptly.

It is our purpose to draw attention to the ocular manifestations of Wernicke's disease, on the basis of the study of five cases, and to point out the manner in which they may be utilized in the diagnosis of the condition.

In 1881, Carl Wernicke [3] described a fatal illness of sudden onset, characterized by a triad of signs: somnolence, ataxia of gait, and ophthalmoplegia. Retinal hemorrhages and swelling of the optic discs were also said to be present. Wernicke described focal vascular lesions, which he considered inflammatory in nature, symmetrically located in the gray matter around the third and fourth ventricles and the aqueduct of Sylvius. Accordingly, he named the condition "acute superior hemorrhagic encephalitis."

The numerous reports since Wernicke's original description have considerably amplified and modified the concept of the disease clinically, pathologically, and etiologically.† The disease is now generally regarded as due to a nutritional deficiency with specific lack of thiamine. Although described predominantly in alcoholics, the disease is not due to the neurotoxic effect of alcohol per se. Contrary to Wernicke's original description, the morbid anatomical changes are disseminated widely throughout the brain stem and are characterized by destruction of both nerve cells and nerve fibers. Nor are hemorrhages either constant or necessarily prominent, as suggested by Wernicke's title.

In addition to the ocular manifestations, the signs of importance are the mental disturbances and the ataxia. The former take the form of a quiet confusional state,

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* References 1 and 2.

† References 4, 5, 6, 7, 8, and 9.

which, in the majority of instances, resolves itself into a Korsakoff psychosis. The ataxia is essentially one of stance and gait, individual movements of the limbs being relatively unaffected. Peripheral neuropathy is a frequent concomitant and, if severe enough, may mask the ataxia.

The usual ocular motor signs consist of (1) nystagmus that is both horizontal and vertical, (2) paralysis of the external recti, and (3) paralysis of conjugate gaze. Pupillary disturbances, ptosis, and funduscopic abnormalities are distinctly rare, though reported from time to time.

CASE 1.—*Diplopia, mental confusion, and ataxia of one week's duration occurring in an alcoholic.*

D. M. (#777937), a 50-year-old former janitor, was admitted to the hospital because of inability to walk, of five days' duration, and confusion and "crossed-eyes," of two days' duration.

A history from his wife and other relatives revealed that he had been an excessive drinker for many years. His work had progressively deteriorated until he took to stoking furnaces, and even this job was abandoned six months prior to his admission. Latterly he had stayed at home, drinking excessively and eating poorly. Details regarding his dietary intake were unavailable, but his weight decreased from 145 to 116 lb. (65.8 to 52.6 kg.) in the six-month period.

Examination on admission revealed a patient who was thin and unkempt, but otherwise with no general medical abnormalities. He was for the most part indifferent and apathetic, but was easily aroused and responded readily. There was gross disorientation in place and time; he had no concept of the nature of his illness, misidentified the examiner, and confabulated spontaneously. A minute after an interview he could neither recall having seen the examiner that day nor give an account of the conversation. Despite his thinness, motor power was adequate. Sensation was quite normal; but his knee jerks could be obtained only with reinforcement, and the ankle jerks were absent. The plantar response was flexor.

His gait was grossly abnormal: He walked on a wide base, with short, uncertain steps, and there was marked staggering, especially on attempting to turn or sit down in a chair.

There was an almost complete bilateral sixth nerve paralysis. On conjugate gaze to either side, a coarse nystagmus developed in the adducting eye, and the range of adduction was not quite complete. There was no impairment of upward and downward gaze or convergence. Similarly, the pupils and fundi were quite normal on admission.

As part of a nutritional study being carried out by one of us (M. V.), the patient was placed on a diet inadequate in all the B vitamins. On the fourth day of the special diet he was given a large variety of vitamins,‡ exclusive of thiamine, and their administration was repeated on the fifth and sixth days. Despite the addition of these nutrients, he became progressively more apathetic and ataxic.

In addition to the eye signs noted on admission, he developed a paralysis of downward gaze and a vertical nystagmus on upward gaze. On the ninth hospital day he was given thiamine hydrochloride, 100 mg. intravenously, and this dose was continued daily thereafter.

Within four hours of thiamine administration there was a detectable improvement in abduction of the eyes. Within 24 hours the patient was much more alert and responsive; he could abduct both eyes to the extent that only about 3 mm. of sclera showed between the cornea and the outer canthus. He was still unable to sustain lateral gaze, and a coarse horizontal nystagmus was now present in both eyes on attempting this movement. A slight degree of conjugate downward gaze had returned by this time, and vertical nystagmus had disappeared.

Three days after the institution of thiamine therapy, there was further improvement in his ability to abduct his eyes and sustain lateral gaze, although these functions were not perfect, and he still showed a coarse horizontal nystagmus. Downward gaze was then only slightly limited.

‡ Vitamin A, 65,000 I. U.; Vitamin D_2, 13,000 I. U.; nicotinamide, 50 mg.; riboflavin, 10 mg., pyridoxine, 50 mg., calcium pantothenate, 500 mg., ascorbic acid, 500 mg., and Vitamin B_{12} (intramuscularly), 15 mγ.

For an ensuing six-week period the patient was maintained on the diet deficient in the B vitamins except that thiamine was added. After two to three weeks there was no detectable ocular motor weakness. His horizontal nystagmus and ataxia improved progressively but were present to a mild degree to the end of six weeks. Although he was much more responsive, cheerful, and alert and confabulated more readily than on admission, his memory defect was not significantly altered. Nor was there any change in the memory defect after an additional six-week period, in which a full diet had been given.

Comment.—This case is presented in detail because it characterizes so many of the clinical features of full-blown Wernicke's disease. The illness developed on a background of alcoholism and malnutrition. The outstanding neurologic features were the confusional state, ataxia, nystagmus, sixth nerve paralysis, and paralysis of downward gaze. There was, in addition, a paresis of horizontal conjugate gaze, manifested by the coarse nystagmus in the adducting eye. The initial absence of nystagmus in the abducting eye was attributed to the superimposed lateral rectus paralysis. The disproportionate paralysis of downward gaze is an unusual manifestation of Wernicke's or of any neuro-ophthalmic disease.

Aside from the ataxia and ocular signs, he showed the neurologic defect characteristic of Korsakoff's psychosis, and a mild peripheral neuropathy (as manifest by absence of knee and ankle jerks). Neither of these features is unusual.[9]

Despite the administration of all vitamins exclusive of thiamine, his signs worsened; with the addition of thiamine alone there was a rapid reversal of his ophthalmoplegia; less rapid, but definite, improvement in his apathy, nystagmus, and ataxia, but practically no improvement in his memory.

CASE 2.—*Rapid onset of ataxia, diplopia, nystagmus, and memory defect in a chronic alcoholic.*

L. W. (#750768), a 46-year-old male kitchen helper, was brought to the hospital by his family, with a history of vomiting, difficulty in walking, diplopia, and confusion of several days' duration.

Although always retarded mentally, he had been able to finish elementary school and had, until his present illness, worked steadily at menial jobs. He had been a chronic alcoholic for most of his adult life, his daily intake of recent years having consisted of one quart (1,000 cc.) of wine, several glasses of ale, and few "shots" of whisky. His diet was described as "poor"; it was his habit to drink large quantities of coffee in place of food. Five days prior to admission he was unable to work because of vomiting. The next day he "looked poorly" and was brought home by his employer because of difficulty in walking. Shortly thereafter he complained of persistent double vision. On the day prior to admission the family noticed that he was "talking nonsense." On examination the abnormal signs were found to be limited to the nervous system. He showed considerable mental defect: He mistook the hospital and gave the year as 1945 (actually, 1951). He could give no clear account of his illness, describing all his symptoms as of a month's duration; he could not recall his jobs in proper sequence and reported events of the long past as having occurred recently. He did not confabulate either spontaneously or with provocation. There was no motor, reflex, or sensory defect in his limbs, and heel-to-shin and finger-to-nose testing was performed satisfactorily. Nevertheless, his gait was wide-based, and he would fall to one side or another on attempting heel-to-toe walking.

The eyes showed a coarse horizontal nystagmus on gaze to either side (more to the left than to the right) and vertical nystagmus on upward gaze. There was some limitation of conjugate gaze to either side and a poor opticokinetic response. In addition, there was bilateral abducens weakness, more in the left eye than in the right, and a diplopia corresponding to a greater limitation of the abducting eye on gaze to either side. Visual acuity, fields, fundi, and pupils weer all normal.

The patient's only therapy consisted of the house diet. Three days after admission his diplopia, ocular muscle weakness, and disorder of gaze had cleared completely, although the horizontal and vertical nystagmus was still present.

On the fourth hospital day the horizontal nystagmus was still present on lateral gaze but was not as coarse as on admission, and the vertical nystagmus was inconstant. Ataxia was barely detectable on heel-to-toe walking. There was no significant change in the mental signs.

The patient has been observed for 18 months after his hospital discharge. Six weeks after the onset of his illness there was no longer any ataxia or vertical nystagmus. At the end of the 18-month period a fine horizontal nystagmus on lateral gaze was still present. Over this period the neurologic signs also had shown a slow but progressive improvement; he was working in a satisfactory manner as a handy man in a nursing home. However, mental testing revealed that there was still considerable vagueness of memory, less in degree than, but of the same nature as, that he exhibited originally.

Comment.—The combination of ocular motor weakness, nystagmus, ataxia, and confusion occurring in an alcoholic taking a deficient diet is characteristic of Wernicke's disease. All these features were much the same as, but less marked in degree than, those in the preceding patient. The abnormal mental state, consisting of vagueness of memory and the transposition of events out of their temporal sequence, is quite characteristic of a mild degree of Korsakoff's psychosis and is frequently seen as a stage in the recovery from the severer form of the disease. It is also noteworthy that considerable improvement in the mental state occurred, allowing the patient to resume a normal place in society. The ocular and gaze palsies disappeared after several days of house diet, although a fine nystagmus persisted for 18 months.

CASE 3.—*Ataxia of gait, bilateral sixth nerve paralysis, nystagmus, mental disturbances, and mild polyneuropathy occurring in an alcoholic; prompt disappearance with adequate diet.*

M. P. (#514955), a 47-year-old woman, was brought to the hospital by her husband. He reported that five days prior to admission she stumbled and fell and that, although her injuries were minimal, she had been unable to walk since that time.

One year prior to admission she gave up stenographic work. Her already heavy alcoholic intake was increased, although the exact amount could not be determined. In the past year she had lost at least 20 lb. (9.1 kg.), the result of an irregular and greatly diminished food intake. For two months prior to admission she was said to have eaten practically nothing.

Examination revealed a wide variety of signs associated with malnutrition in alcoholics—thin limbs, loose dry skin, hyperkeratosis of the elbows, perifollicular hemorrhages of the thighs and legs, pigmentation of the forehead, acne rosacea of the face, and an enlarged liver.

She was disoriented in time and thought she was in another hospital. She could not recall the correct date after an interval of three minutes. She confabulated readily, telling of being discharged from another hospital a few days before, being home overnight, and so forth. Her gait was broad-based; her steps were short and uncertain, and she was completely unable to walk a straight line. There was mild generalized muscle weakness, most definite in the dorsiflexors of the feet. Deep reflexes were absent, and the plantar response was flexor. There was blunting of pain, touch and temperature, and vibration sense below the knees, and position sense was impaired in the toes.

The eyes showed a mild bilateral sixth nerve palsy and mild inability to maintain conjugate lateral gaze. There was a coarse horizontal nystagmus on gaze to either side, with inability to maintain conjugate lateral gaze, and less coarse horizontal nystagmus on upward gaze. The house diet and supplementary B vitamins constituted the only treatment which the patient received. In three to four days her sixth nerve paralysis had disappeared, and in the ensuing four weeks there was disappearance of her vertical nystagmus as well. Concomitantly, the horizontal nystagmus became less coarse, and the ataxia elicitable only on attempted heel-to-toe walking. Her nutritional state improved, as did her mental state. She was better oriented; her memory span increased, and she no longer confabulated.

Comment.—This patient presented the characteristic signs of Wernicke's disease, as well as of a mild peripheral neuropathy. The mode of recovery was also characteristic. The sixth nerve weakness was readily reversible; the nystagmus and

ataxia improved, but slowly. The mental signs were the most refractory; but here, too, she became less confused, her memory span lengthened, and she no longer confabulated.

CASE 4.—*Anorexia, vomiting, paralysis of conjugate gaze, and confusion occurring in an alcoholic.*

H. W. (#650426) was a 39-year-old woman who had worked for years as a waitress in a bar and had taken considerable amounts of alcohol during this time, with the occasional development of "morning shakes." Recently the patient had developed anorexia, vomiting, forgetfulness, and confusion. There was also some paresthesias of the lower limbs.

Examination showed a tremor of all extremities, inability to walk, and diminished knee and ankle jerks. Mentally, the patient was oriented but easily confused and showed defective memory of recent events. At the first examination there was practically complete paralysis of conjugate gaze to the left and limitation of conjugate gaze to the right to approximately 10 degrees. Vertical gaze was normal, but a vertical nystagmus developed on attempted gaze to the left. The opticokinetic response was absent bilaterally but normal vertically. Rotation in a Bárány chair elicited a somewhat diminished horizontal nystagmus but a brisk vertical nystagmus. Convergence was well performed. The pupils and the corneal sensation were normal. The fundi were negative. Visual acuity was practically normal.

Examination some hours later showed the same ocular abnormalities, but they were less marked, even though the patient was not known to have received any thiamine. The patient was aware of this improvement and volunteered that the eye movements had shown similar spontaneous variations from time to time.

The patient was put on an adequate diet containing thiamine. Within two days there was practically full movement of the eyes on gaze to either side but a slight residual nystagmus on gaze to the left. The opticokinetic response on rotation of the visual field to the left was still abortive, although it was normal on rotation to the right.

Comment.—This case is another that may be considered typical of the alcoholic variety of Wernicke's disease. The paresthesias in the legs were presumably manifestations of an associated polyneuropathy which, although not strictly part of the Wernicke complex, is frequently associated with it, as evidenced by Cases 1 and 3. The fact that nystagmus was not a conspicuous feature in this case is in accord with the observation that as the paralysis of conjugate gaze becomes more profound the nystagmus becomes less striking.

Although the lesion in the present case must be presumed to have been bilateral, it was definitely asymmetric, with greater involvement of the left side. With recovery the most persistent neuro-ophthalmic abnormalities were the nystagmus in the extreme horizontal gaze and the deficiency of the opticokinetic response.

CASE 5.—*Ataxia, dysarthria of speech, and paralysis of divergence and of the near reflex occurring with malnutrition (nonalcoholic variety).*

This case, L. C. (#486192), has been described previously,[10] so that only a summary need be given here. The patient, aged 29, developed a profound malnutrition following a series of gastrointestinal disturbances, culminating in an ileotransversostomy. He was thought to have multiple vitamin deficiencies for several months after the operation, and during this time he developed lethargy, vertigo, incoordination of arms and legs, diplopia, inability to see at near, and difficulty with speech.

On examination he was found to have marked ataxia of all four extremities, gross dysarthria of speech, and a disorder of his eyes. His reflexes were normal, and he had no mental symptoms. The eyes showed at first typical divergence paralysis with mild horizontal nystagmus on gaze to either side, vertical nystagmus on upward gaze, associated weakness of convergence, and areflexia of the pupils for near.

With vitamin B therapy there was prompt recovery from ataxia, from the nystagmus, and from the divergence paralysis, but an apparent unmasking of paralysis of the near reflex, which persisted for several months. The latter consisted of gross insufficiency of convergence, absence of pupillary reaction for near, and almost complete paralysis of accommodation.

Comment.—The development of nystagmus and ataxia on a background of severe malnutrition, together with their prompt reversal by vitamin B therapy, is diagnostic of Wernicke's disease. The absence of mental symptoms, aside from lethargy, is to be seen in only a minority of the patients; ataxia of individual movements of limbs (in contrast to that of gait) and dysarthria, such as this patient had, are distinctly rare but have been observed. The most unusual, and, to our knowledge, the unique, feature of this case is the combined paralysis of divergence and of the near reflex occurring as part of Wernicke's disease.

GENERAL COMMENT

The first four patients of this series represented the clinical manifestations of Wernicke's encephalopathy in alcoholics. They all showed a group of characteristic ocular signs, consisting of nystagmus, paralysis or paresis of the sixth nerves, and varying degrees of paralysis of the conjugate mechanisms. Yet even this small group showed considerable diversity within itself. The paralysis of conjugate movements varied from merely a nystagmus on extreme gaze in one direction to a complete loss of ocular movement in that direction. This applied to both horizontal and vertical movements, though abnormalities of the former were commoner. With this involvement of the conjugate mechanism there was varying sixth nerve paralysis. The ocular manifestations were bilateral but not always symmetrical. The negative findings were also noteworthy in these cases: absence of ptosis, pupillary disturbance, papilledema, retinal hemorrhages, and retrobulbar neuropathy.

Most of the ocular findings in this small group of patients are representative of what has been found by others in larger series. De Wardener and Lennox,[11] who observed this syndrome in 52 prisoners of war, reported nystagmus as the earliest ocular sign. In another series, of 86 cases, Victor and Adams[9] found nystagmus to be the commonest, and often the only, abnormal eye sign. Abducens weakness was also present in a high proportion of cases. These authors noted as well the rarity of other ocular signs.

Nystagmus cannot, of course, be considered pathognomonic of Wernicke's encephalopathy, even when associated with a definite history of alcoholism. Thus, it has been found in acute inebriation[12] and may occur as a transient phenomenon in the period of abstinence following inebriety.§ Even when all the ocular signs, consisting of nystagmus, paralysis of the sixth nerves, and conjugate mechanisms, are present, they cannot unreservedly be said to indicate Wernicke's encephalopathy. These signs may occur with a wide variety of brain stem lesions (vascular, demyelinating, neoplastic, or inflammatory) provided these lesions affect pertinent parts governing the ocular mechanisms. A combination of nystagmus and ataxia without vertigo frequently occurs in barbiturate intoxication or with cerebellar lesions; these states, too, are common in alcoholics. What is characteristic of Wernicke's encephalopathy is the association of the eye signs with ataxia and the mental disturbance of the type described in the introductory paragraphs. This triad of clinical signs, evolving

§ Victor, M., and Adams, R. D.: Unpublished data.

rapidly on a background of alcoholism and malnutrition, is so distinctive that there need be no difficulty in making an accurate diagnosis. Further confirmation of the diagnosis may be obtained by observing the prompt improvement in the eye signs with thiamine administration.

The fifth patient in this series represents the nonalcoholic variety of Wernicke's encephalopathy, having developed the disease as part of a profound state of malnutrition. His case was unique in that he had a predominant involvement of the near-far focusing mechanism, which does not appear to have been reported in other patients with this disease. Yet its response to the B vitamins undoubtedly makes it a part of this entity.

The division of Wernicke's encephalopathy into alcoholic and nonalcoholic types is not a fundamental one. In the extraordinary epidemics reported by de Wardener and Lennox [11] and Cruickshank [6] in British prisoners of war, the similarity to the alcoholic variety was striking as regards both the mental symptoms and the ocular signs.

As has already been indicated, the specific deficiency responsible for the neuro-ophthalmic manifestations is that of thiamine. In the British prisoners of war, cases of Wernicke's disease appeared as early as six weeks after the abrupt change from an adequate diet to one consisting mainly of polished rice; during this period, the ratio of thiamine was below the critical level of 0.3 mg. to 1,000 nonfat calories in the diet.[13] The striking reversal of the ophthalmoplegia with thiamine leaves little doubt as to the specificity of this vitamin. In a study designed to test specifically the effect of various vitamins on the clinical manifestations of Wernicke's syndrome,[8] it was found that the ocular palsies cleared considerably in from one and a quarter to six hours. Furthermore, the dose required to produce this salutory effect need be only as little as 2 to 5 mg.|| But complete range of ocular movement may not be regained for several days, and horizontal nystagmus may persist for years. The fact, however, that there is such improvement with thiamine indicates that most of the eye abnormalities are not dependent on irreversible pathologic changes. In the few pathologic studies of patients with Wernicke's disease who were known to have ophthalmoplegia during life, destructive lesions of the ocular motor nuclei were infrequent.¶

SUMMARY

Wernicke's disease has received little attention in the ophthalmic literature, even though the eye signs are its most constant and characteristic abnormality. The usual eye signs are sixth nerve paralysis, horizontal and vertical nystagmus, and varying palsies of conjugate gaze. The prime nonophthalmological abnormalities are ataxia of gait, confusional states of the Korsakoff variety, and polyneuropathy.

The disease results from a nutritional disturbance with specific lack of thiamine. Administration of thiamine results in prompt reversal of the sixth nerve paralyses, less striking, but nevertheless definite, improvement in the nystagmus and ataxia, and least change in the mental state.

Five patients are described, four of whom had nutritional deficiencies secondary to chronic alcoholism and one from disease of the gastrointestinal tract. The four

|| References 8 and 6.

¶ References 5 and 14.

had the typical manifestations of ophthalmoplegia, ataxia, and confusion, while the fifth had the unique occurrence of paralysis of the near-far focusing mechanisms with ataxia and dysarthria but no mental disturbance.

REFERENCES

1. Ecker, A. D., and Woltman, H. W.: Wernicke's Disease: A Neuro-Ophthalmic Syndrome of Nutritional Deficiency, Proc. Staff Meet., Mayo Clin. **14**:520-524 (Aug. 6) 1939.

2. Kravitz, D., and Stockfisch, R. H.: Wernicke's Disease (Encephalitis Hemorrhagica Superioris), Am. J. Ophth. **28**:596-600 (June) 1945.

3. Wernicke, C.: Lehrbuch der Gehirnkrankheiten, für Aertze und Studirende, Kassel and Berlin, T. Fischer, 1881, p. 229.

4. Spillane, J. D.: Nutritional Disorders of the Nervous System, Baltimore, Williams & Wilkins Company, 1947, p. 82.

5. Riggs, H. E., and Boles, R. S.: Wernicke's Disease: A Clinical and Pathological Study of 42 Cases, Quart. J. Stud. Alcohol **5**:361-387 (Dec.) 1944.

6. Cruickshank, E. K.: Wernicke's Encephalopathy, Quart. J. Med. **19**:327-338 (Oct.) 1950.

7. Victor, M.; Hope, J. C, and Adams, R. D.: A Clinical Study of Wernicke's Disease, Tr. Am. Neurol. A. **77**:178-182, 1952.

8. Phillips, G. B.; Victor, M.; Adams, R. D., and Davidson, C. S.: A Study of the Nutritional Defect in Wernicke's Syndrome: The Effect of a Purified Diet, Thiamine, and Other Vitamins on the Clinical Manifestations, J. Clin. Invest. **31**:859-871 (Oct.) 1952.

9. Victor, M., and Adams, R. D.: The Effect of Alcohol on the Nervous System, A. Res. Nerv. & Ment. Dis., Proc., 1952, to be published.

10. Cogan, D. G.: Divergence Paralysis and Paralysis of the Near Reflex Associated with a Malnutrition Syndrome (Presumably Wernicke's Polioencephalitis), A. M. A. Arch. Ophth. **46**:436-437 (Oct.) 1951.

11. de Wardener, H. E., and Lennox, B.: Cerebral Beri-Beri (Wernicke's Encephalopathy), Review of 52 Cases in Singapore Prisoner-of-War Hospital, Lancet **1**:11-17 (Jan. 4) 1947.

12. Howells, D. E.: Nystagmus and Other Eye Signs in Acute Alcoholism, Brit. M. J. **2**:862-864 (Oct. 11) 1952.

13. Williams, R. R., and Spies, T. D.: Vitamin B_1 (Thiamin) and Its Use in Medicine, New York, The Macmillan Company, 1938.

14. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy (Policoencephalitis Haemorrhagica Superior): Its Alcoholic and Non-Alcoholic Incidence, J. Path. & Bact. **48**:245-262 (March) 1939.

CONTACT LENSES IN APHAKIA

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THE PROBLEMS of aphakic vision have plagued the cataract patient and the ophthalmologist for a long time. Much has been written on the subject which need not be reviewed here. In 1934 [1] Cowan discussed the problem, and Kirby [2] has summarized it well in his text. The subjective sensations were strongly emphasized in a recent dramatic anonymous editorial.[3]

In addition to the ordinary problems of aphakic vision, those posed by the patient with unilateral aphakia and an essentially normal fellow eye seem so great that many ophthalmologists have opposed operation on monocular cataracts.

The recent successful introduction of intraocular acrylic prostheses * has rekindled interest in this entire question. Optically, the new technique would appear to be the most nearly ideal arrangement, particularly for the patient with monocular aphakia. It is not our province to assess the practical risks of such an operation, nor can we, or any one, evaluate the late complications until many cases have been carefully studied over a longer period. It is the purpose of this paper to point out that optical results which are at least nearly as satisfactory can be obtained with contact lenses without abandoning the safety of known and tried operative methods or adding unknown and, at present unassessable, long-term risks. We do not wish in any way to criticize the pioneers who are studying intraocular acrylic lenses; we desire merely to point out that there are other methods available to the surgeon who is not eager to jump on the experimental band wagon and to the patient for whom the new technique is not suitable.

Correction of aphakia with contact lenses is not new. It has been described before, and we have used it for 10 years. However, it is not as widely used as its potentialities would seem to indicate, and in some quarters it seems to be virtually unknown. We have been unable to find in the literature a comprehensive discussion of the use of the various types of currently available lenses.

It has been our clinical experience that patients with monocular aphakia, when fitted with a suitable contact lens for the aphakic eye, use both eyes together with comfort and satisfaction. It is common for them to complain of a loss of depth and three-dimensional sensations when the lens is omitted and to state that they do not see properly without it, even though the normal eye may have perfect acuity.

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* References 4 and 5.

It seemed worth while, therefore, to study some of the patients using contact lenses for correction of aphakia from the standpoint of comfort, tolerance, fusion, stereopsis, and image-size difference.

TYPES OF LENSES

Our earlier patients were fitted with conventional contact lenses made by the molding technique. In the last few years, corneal lenses and Lacrilenses have been used. Visual results are essentially the same for the various types. Tolerance, expense, and ease of fitting vary. In general, the older type of molded lens, with a scleral lip, has been abandoned because of shorter wearing periods and difficulty with solutions. However, some patients have been wearing these lenses with considerable satisfaction for long periods. One patient with bilateral aphakia wore her pair all day, every day, for eight years, finally arriving at the autopsy table with them on, when she died of intestinal carcinoma. Unfortunately, the corneas could not be obtained for histological study, but no biomicroscopic changes had been observed over the eight-year period.

Corneal lenses have been used in most of the recent cases because stock lenses can be fitted without molding, because no artificial fluids are necessary, and because

TABLE 1.—*Wearing Time of Contact Lenses (Thirty-Nine Patients)*

Over 10 hr.	17
6-10 hr.	4
2-6 hr.	1
Under 2 hr.	1
Variable or unknown	6
Discontinued	10

of the smaller expense to the patient. Thirty-nine aphakic patients fitted with these lenses have obtained satisfactory vision, but 10 have discontinued their use, for various reasons.

Only two patients have been fitted with the Lacrilens for aphakia, but both wear the lenses satisfactorily for indefinite periods. This type of lens eliminates the solution problem but does require molding and is more costly and exacting to fit. It may be that this lens, or some modification of it, will solve the difficulties of some of the patients who are not completely happy with the corneal type.

The length of time that aphakic patients wear their lenses is rather longer than the experience with other conditions and compares favorably with the wearing time in many cases of keratoconus. These data are summarized in Table 1. Experience with patients wearing contact lenses for cosmetic purposes show much less tolerance in phakic eyes. Since our patients do not show impairment of corneal sensation, we must conclude that the psychic drive to obtain better visual efficiency is the controlling factor.

MONOCULAR APHAKIA

A most important indication for contact lens correction is the patient who has monocular aphakia with normal or nearly normal vision in the other eye. Many of these patients can be restored to useful binocular vision. Some obtain binocular vision as soon as the lens is fitted; some require a little training and practice; some have so much muscle imbalance that prisms are required, and one has had to have

muscle surgery in order to achieve binocularity. It has been our experience that patients who once had binocular vision but have drifted into heterotropia with a monocular cataract can usually be brought back to orthotropia and fusion with contact lens correction. In many of these cases it is helpful to prescribe temporary prisms in the minimal amount necessary to give fusion, reducing the amount in graded steps as amplitude is regained. The amount of prism correction required for the patient to fuse the Worth four-dot test has proved to be a better guide than the Maddox-rod or the prism-cover test. Where there is a significant refractive error in the normal eye, contact lens correction for it may be used.

FUSION

It has been asserted by Cowan[6] that fusion cannot be obtained in monocular aphakia, "whether it is corrected with a spectacle lens, a contact lens, or a minifying lens." He maintains that diplopia may be avoided by monocular suppression but that single binocular vision is not obtained. Our experience is in such disagreement with this notion that it seems worth while to cite some of the results.

TABLE 2.—*Results in the Worth Four-Dot Test (Thirty Patients)*

Fusion		25
	Without prisms	14
	With prisms	11
No fusion		5

TABLE 3.—*Fusion on Synoptophore (Sixteen Patients)*

First-grade	16
Second-grade	16
Third-grade	12

A series of 37 patients with acuity of 20/30 or better in the aphakic eye and 20/30 or better in the normal eye have been followed long enough to form some conclusions. From the patient's standpoint, ability to use both eyes together comfortably is the important factor. It is interesting to compare the binocular functions of these patients as measured by the Worth four-dot test and the standard tests in the synoptophore. Not all could be reached for follow-up study. The results are given in Tables 2 and 3. Twenty-five out of 30 patients were able to fuse the four-dot test. Sixteen out of 16 patients had first-grade, 16 second-grade, and 12 third-grade fusion with amplitude on the synoptophore. The patients, however, were more interested in their subjective sensations and their ability to use the two eyes together in a manner which met their individual standards of normal vision. Twenty-seven out of 37 were able to do this.

Mr. Salvatori,† of Obrig Laboratories, has collected information on 75 aphakic patients fitted for various ophthalmologists. Of these, 62 had monocular aphakia, and 60 achieved apparently satisfactory binocular vision, although fusion studies are not available. Six of these had initial diplopia, which disappeared after prism exercises.

† Salvatori, P. L.: Personal communication to the authors.

ANISEIKONIA

Theoretical calculations would suggest that even with contact lenses these patients should have excessive amounts of image-size difference. Dr. Arthur Linksz has measured this factor in seven patients; and the results, together with the detailed fusion test results, in these cases are given in Table 4. It is interesting to note the relatively high amounts of aniseikonia, which agree closely with theoretical calculations, in patients who are sustaining good binocular vision with comfort.

TABLE 4.—*Aniseikonia and Fusion (Seven Patients)*

Case	Size Diff.	Worth Four-Dot	Fusion Grade
Z	8%	+	III
D	4%	+	III
C	9%	+	III
H	10%	+	III
G	8½%	+	III
P	7%	+	III
S	6%	?	III

SUMMARY AND CONCLUSIONS

Many of the difficulties of aphakic vision, including image distortion, visual field limitation, astigmatism, and heavy, unsightly spectacles, can be obviated by the use of contact lenses. Patients with monocular aphakia and a normal eye can have useful binocular vision restored safely and with relative ease through contact lenses. It is suggested that wider use of this device be made in aphakic patients.

REFERENCES

1. Cowan, A.: Some Factors Concerned in the Correction of Aphakia, Arch. Ophth. **12**:571-579, 1934.

2. Kirby, D. B.: Surgery of Cataract, Philadelphia, J. B. Lippincott Company, 1950, pp. 635-648.

3. The Adjustment to Aphakia, Editorial, Am. J. Ophth. **35**:118-122, 1952.

4. Ridley, H.: Intra-Ocular Acrylic Lenses After Cataract Extraction, Lancet **1**:118-121, 1952.

5. Ridley, H.: Intra-Ocular Acrylic Lenses: A Recent Development in Surgery of Cataract, Brit. J. Ophth. **36**:113-122, 1952.

6. Cowan, A.: Monocular Aphakia, A. M. A. Arch. Ophth. **49**:473-474, 1953.

THE H-R-R POLYCHROMATIC PLATES

I. A Test for the Detection, Classification, and Estimation of the Degree of Defective Color Vision

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FOR SOME years it has been realized by those concerned with testing for anomalies of color vision that there is an urgent need in office, school, clinic, and in industrial and military examinations for a practical test which goes beyond the mere separation of those with defective color vision from those whose color vision is normal. In addition to this, it is important to be able to determine the type of defect present and its approximate extent in order to judge whether the defect constitutes a real handicap to the subject in his daily life and in the performance of his chosen work. In the H-R-R Plates we are offering such a comprehensive test. It is in the form of a book containing 21 color plates of the pseudoisochromatic type. The only auxiliary equipment is the proper illuminant. The test can be administered in three minutes or less and is suitable for children, illiterates, and foreigners. It serves not only as a screening device but as a device to show both type and extent of the defect.

The development of this test has been a subject of major interest to us for the past 10 years. The work was begun in 1943 in conjunction with the testing program of the ISCC Subcommittee on Color Blindness.* The first edition of the plates was handmade and showed sufficient promise to warrant the color printing of a small edition so that copies could be distributed to cooperating laboratories and testing stations. This printed edition was prepared under our direction by Carl E. Foss, color consultant, the work being supported by the Office of Naval Research under contract N8-onr-70200. It has been checked by us on more than 600 subjects with normal color vision and more than 150 subjects with defective color vision of different types and different degrees of defect. This survey has strengthened our conviction that a series of plates of this kind has great practical value. We say this in spite of the fact that in printing this second edition there occurred some defects in registration which provided slight contour clues to the reading of some of the

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* Members of that committee, particularly Judd, Nickerson, Foss, Farnsworth, and Granville, gave us help and recommendations.

symbols. The survey further served to suggest certain improvements in the design and arrangement of the symbols. The defects in registration will be eliminated and the improvements incorporated in a third edition of the test, now in production by the American Optical Company. We believe that the colors and values used are satisfactorily adjusted, particularly those for testing red-green discrimination.

The present report is based on our experience with the small edition of the test prepared by Mr. Foss. It will deal only with the H-R-R Plates as a device for testing red-green vision, since the number of subjects who have made errors in the blue-yellow series is too small to warrant conclusions as to the value of the plates of this series.

THE H-R-R POLYCHROMATIC PLATES

On a functional basis, color vision tests may be classified into four categories:

1. Simple screening tests, designed to separate subjects with defective color vision from those with normal color vision

2. Qualitative diagnostic tests, designed to classify the type of defective color vision

3. Quantitative diagnostic tests, designed to indicate the extent of the defect in color vision

4. Aptitude, or special tests (luminous signal tests, lantern tests, fog lights, running lights —aviation, marine, and railroad; aptitude tests for special vocations, etc.), designed to determine a subject's relative fitness for a particular vocation. These tests may usefully be applied to those with normal color discrimination as well as to those with color anomaly. It must be remembered that the results of tests utilizing reflected light, which ordinarily involve large retinal images of low or medium brightness, may be applied only with reservations to situations demanding recognition of luminous signals which yield small retinal images of high brightness.

Utilizing this classification, the H-R-R Test consists of a series of polychromatic plates encompassing the first three categories listed above. It is divided into four parts: (1) three demonstration plates showing resp. two, one, or no design on a plate; (2) five screening plates (Plates 1-5); (3) nine qualitative and quantitative plates for diagnosing red-green defects (Plates 6-14), and (4) four qualitative and quantitative plates for diagnosing blue-yellow defects (Plates 15-18).

The test is of the pseudoisochromatic type; that is, to subjects with defective color vision the background and the design to be discriminated are pseudoisochromatic (apparently of the same color), and the design is not seen by such people. In the H-R-R Plates only confusions of color with gray are utilized. For all plates of the test a single mask was used, consisting of a pattern of small discs varying in size and value (brightness). This pattern is repeated in each quadrant of the plates. Certain of these discs are colored so as to form geometrical designs, and the remainder are neutral gray. The hues of the designs were critically selected to differentiate between the two types of red-green defect and the two types of blue-yellow defect. For example, a green and a red-purple are used which are confused with gray by the deutan † but not by the protan † type of observer with red-green deficiency; also, a blue-green and a red which are confused with gray by the protan but not by the deutan type. Therefore, the subject is a deutan if he misses green or red-purple designs but sees blue-green or red ones; on the contrary, the subject is a protan if he misses blue-green or red designs but sees green or red-purple ones

† Protan is a collective term for protanomalous and protanopic subjects; deutan, for deuteranomalous and deuteranopic subjects. These terms were suggested by Farnsworth and, because of their convenience, have been accorded wide usage in this country.

(qualitative diagnosis). To make this diagnosis possible, one of the critical designs must be missed and the other must be seen. In successive plates the designs in these critical hues appear in a graded series of increasing chroma to indicate the extent of the defect (quantitative diagnosis). When, for example, only designs of low chroma are failed, the defect must be less marked than when designs of both low and high chroma are failed. The presentation of the critical hues in graded steps of chroma also permits the qualitative diagnosis to be made whether the defect be mild, medium, or strong. If the pair of critical colors is presented in medium chroma only, as is usual in pseudoisochromatic plates, those whose defect is mild may see both designs and those whose defect is strong may see neither. In such cases the qualitative diagnosis would not be indicated, and the subject is not classified as to type of defect.

Eight principal hues are used varying in chroma and value, and four values of neutral gray. The colors are accurately controlled for chromatic qualities and permanence. The hues and values for the protan and deutan types of red-green deficiency were carefully adjusted experimentally to the average neutral points of a group of dichromatic subjects of these two types.‡ The hues and values for the tritan and tetartan types of blue-yellow deficiency (the latter theoretical) were adjusted in accordance with Judd's description of the neutral points of these two types.[1] As already indicated, all background patterns are identical and thus yield no clues for memorization or coaching. The symbols are simple geometrical designs (square, circle, triangle) which are familiar to foreigners, illiterates, and children.

The plates are printed with plastic paints containing no linseed oil or printing inks. One of the most serious defects of printed tests for color vision has been the impermanence of the colors and their deterioration with age. This is an inescapable factor in all printing involving the use of linseed oil inks. Another serious defect is the variability of the color with succeeding copies in a production run. Both these defects, we are assured by our color consultant, Mr. Foss, have been satisfactorily overcome in this set of plates, in which paints in a plastic base rather than inks are used.

Any critical test utilizing reflected light is dependent upon the illumination used.[2] It is mandatory that this test be given under 10 to 60 f.-c. of Illuminant CIE-C, or a close approximation to this. We recommend the Easel Lamp,§ designed for color vision testing at the New London laboratory.[3]

A sample sheet for recording the results of tests with the H-R-R Plates is shown in Chart 1. A record showing defective red-green vision is interpreted as follows: Type of defect (qualitative diagnosis) is obtained by a comparison of the subject's responses with those listed in the two columns "Protan Reads" and "Deutan Reads." Preponderance of responses similar to those in either one or the other of these columns will rate the subject as protan or deutan. Extent of defect (quantitative diagnosis) is based on the last series of plates (mild; medium; strong) in which errors occur. Extensive scattered errors may indicate malingering, monochromasy, or low color-discrimination approaching monochromasy.

‡ The experimental work was done under 25 f.-c. of illumination provided by a large Macbeth Daylight lamp, color temperature 6750° K.

§ Manufactured by Macbeth Daylighting Corporation, Newburgh, N. Y.

RECORD SHEET
for use with
H-R-R PLATES

Name _____ Date _____ Examiner _____

Address _____ Tel. _____ Occupation _____

SCREENING TEST

	Plate No.	Normal Reads	Subject Reads
B-Y Defect	1	s c	___ ___
	2	t s	___ ___
	3	c t	___ ___
R-G Defect	4	t s	___ ___
	5	c t	___ ___

Any error in Plates 1-5 indicates defective color vision. No further error in Plates 6-18 indicates Mild Defect, unclassified as to type.

R-G DEFECT - 2

	Plate No.	Normal Reads	Protan Reads	Deutan Reads	Subject Reads
Medium R-G Defect	10	t s	t -	- s	___ ___
	11	t s	t -	- s	___ ___
	12	s c	s -	- c	___ ___
Strong R-G Defect	13	t s	t -	- s	___ ___
	14	s c	s -	- c	___ ___

Errors in Plates 10-12 but not in 13-14 indicate Medium R-G Defect. Errors in Plates 13-14 indicate Strong R-G Defect.

R-G DEFECT - 1

	Plate No.	Normal Reads	Protan Reads	Deutan Reads	Subject Reads
Mild R-G Defect	6	s c	s -	- c	___ ___
	7	s c	s -	- c	___ ___
	8	c t	c -	- t	___ ___
	9	s c	s -	- c	___ ___

Errors in Plates 6-9 but not in 10-14 indicate Mild R-G Defect.

B-Y DEFECT

	Plate No.	Normal Reads	Tritan Reads	Tetartan Reads	Subject Reads
Medium B-Y Defect	15	s c	s -	- c	___ ___
	16	c t	c -	- t	___ ___
Strong B-Y Defect	17	s c	s -	- c	___ ___
	18	t s	t -	- s	___ ___

Errors in Plates 15-16 but not in 17-18 indicate Medium B-Y Defect. Errors in Plates 17-18 indicate Strong B-Y Defect.

Screening Diagnosis: (Plates 1-5) Normal ☐ B-Y Defect ☐ R-G Defect ☐

Classification:
Type: Protan ☐ Deutan ☐ Tritan ☐ Tetartan ☐
Extent: Mild ☐ Medium ☐ Strong ☐

Subject's Signature _____

INTERPRETATION: Type of red-green defect is indicated by a preponderance of subject's responses similar to those listed under either "Protan Reads" or "Deutan Reads"; type of blue-yellow defect, similar to those listed under "Tritan Reads" or "Tetartan Reads".
Extent of defect is based on the last series of plates (mild-medium-strong) in which errors occur. Extensive scattered errors may indicate malingering, monochromasy or Low Discrimination approaching monochromasy.

Chart 1.—Sample sheet for recording results of tests with the H-R-R Plates.

EVALUATION OF THE H-R-R POLYCHROMATIC PLATES

In this section is given an evaluation of the H-R-R Plates (1) as a screening device to separate those with defective red-green vision from those with normal color vision, (2) as a device to classify the type of defect (qualitative diagnosis), and (3) as a device to indicate the extent of defect (quantitative diagnosis).

The subjects used for this evaluation were not selected on the basis of a statistical survey. They included patients referred to us by ophthalmologists and men rejected by the armed forces because of defective color vision, also subjects obtained from the Vanderbilt Clinic and from New York colleges and high schools. All subjects, except those from the high schools, were tested in the laboratory on a battery of color tests.‖ These included subjects with both normal and defective color vision. In the high schools, however, where suitable conditions could be

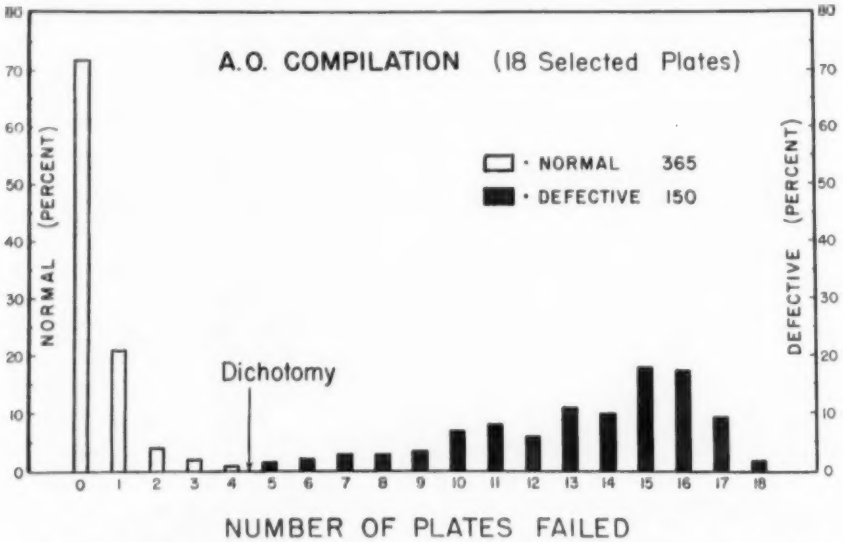

Chart 2.—Results of tests with the Revised Selection of A. O. Plates, showing dichotomy between number of plates failed by subjects with normal color vision and those failed by subjects with defective red-green vision.

provided for the administration of pseudoisochromatic tests alone, only those found to have defective color vision on the basis of these tests were referred to the laboratory for the more complete study.

1. *The H-R-R Test as a Screening Device.*—For this evaluation, in case of the high school students, we in general accepted the Revised Selection of A. O. Plates, approved by the ISCC Subcommittee on Color Blindness, as providing an adequate device for screening those with defective red-green vision from those with normal color vision. This selection of 18 plates had already been studied by us in conjunction with a large battery of color tests [4]; and when administered in accordance with

‖ The battery included the A. O. Test (Revised Selection, 18 plates), the Ishihara Test (5th edition, 12 plates), the Nagel anomaloscope (Model I), the Navy Lantern (New London model), the Color Threshold Tester (School of Aviation Medicine model), the Farnsworth Dichotomous Test (Panel D-15), and other tests as are indicated in the individual case.

the instructions, it provides an acceptable separation of the two groups with the following interpretation of error score: Incorrect response to four or fewer plates indicates normal red-green vision; incorrect response to five or more plates, defective red-green vision. Chart 2 shows the results on which this interpretation was based. However, in the few cases in which three or four plates were failed, the precaution was taken to administer an additional screening test of the pseudo-isochromatic type: either the Ishihara (fifth edition), allowing incorrect response to three or fewer plates to indicate normal red-green vision,[5] or the Bostrom-Kugelberg, allowing incorrect response to two or fewer plates. On the basis of these criteria, two groups of subjects were available for the present study: (*a*) 630 subjects with normal red-green vision and (*b*) 150 subjects with defective red-green vision.

The H-R-R Test was administered to these two groups, with the result that all subjects with normal color vision made no errors in the low-chroma plates comprising the screening series, and all subjects with defective color vision made some errors in the screening series.

The H-R-R Test, therefore, on the basis of these criteria successfully screens subjects with defective red-green vision from those with normal red-green vision.

Test-Retest Reliability of the H-R-R Plates as a Screening Device: In 238 cases the H-R-R Test was given twice in order to see how reliable the results of a single administration of the test can be considered. To insure a representative sample for this comparison, all subjects studied over a period of time were tested twice until records of 131 subjects with normal and 107 with defective red-green vision on the initial test had accumulated. The group with defective red-green vision included subjects with mild, medium, and strong defects in proportions closely similar to those found in our entire group of 150 such subjects. It is obviously important for this kind of comparison that a representative sample of both the normal and the color-defective population be studied in order to include a typical number of subjects whose color vision is borderline between normal and defective.

The 131 subjects with normal red-green vision were retested on the same day following the administration of one, two, or more tests of color vision. On the retest, 130 were again rated as having normal red-green vision; the remaining subject on retest read incorrectly one of the designs in the screening series of plates and was rated as having mild red-green deficiency. By other tests of the battery this subject was normal, except that with the Nagel anomaloscope he evidenced quick fatigue to green. The 107 subjects with defective red-green vision were retested either on a second day or on the same day after the administration of three or more other tests of color vision. On the retest, 105 were again rated as having defective red-green vision; the remaining 2, whose errors in the first test had occurred only in plates of the screening series, read all designs correctly on the second trial. That the first test gave the correct diagnosis in these two cases was borne out by the results of the other color tests given these subjects.¶

¶ Case A, for example, made five errors on the A. O. Test and three on the Ishihara, passed the Navy and RCAF Lanterns, scored 56 on the Color Threshold Tester, passed the Dichotomous Test, and was rated deuteranomalous on the Nagel anomaloscope. Case B made 10 errors on the A. O. Test and 5 on the Ishihara, passed the Navy and RCAF Lanterns, scored 60 on the Color Threshold Tester, passed the Dichotomous Test, and was rated protanomalous on the anomaloscope.

The test-retest results for the H-R-R Plates as a screening device are given in Table 1. Figures in boldface type show the number of subjects who fell into the same category on test and retest; figures in lightface italic type show the number who shifted category on the retest. This Table shows that the proportion of the group failing one of two testings and passing the other is small (1.3%), thus indicating that the test-retest reliability of the H-R-R Plates as a screening device is very high.

2. *The H-R-R Test as a Device to Classify the Type of Defect (Qualitative Diagnosis).*—For this evaluation we accepted the Nagel anomaloscope as providing a qualitative diagnosis of defective red-green vision under the two types: deutan and protan. We did this because this instrument has a higher degree of standardization and of acceptance for yielding this diagnosis than any other test at present available. The anomaloscope was used as recommended by Trendelenburg and Engelking, with the neutral filter placed over the green slit. This method brings the normal match almost to the center of the scale, the significant range of which in our instrument, as in Trendelenburg's,[6] is 0 to 73.# With this technique the group of 150 subjects having red-green deficiency was separated into 90 deutans, 57 protans, and 3 who could not be classified as to type of red-green defect by the anomaloscope.

TABLE 1.—*Test-Retest Results on the H-R-R Plates as a Screening Device* *

		Retest →		
Test		Normal	Defective	Test Totals
↓	Normal	**130**	*1*	131
	Defective	*2*	**105**	107
	Retest totals	132	106	238

* Normal = no errors on Plates 3-5; defective, one or more errors on Plates 3-5.

These three showed, however, a wider-than-normal range of match with the eye unfatigued (resp. 10, 37, and 40 scale divisions) with the center of the range falling within normal limits (resp. 40, 38.5, and 40). The record on the battery of tests for these subjects is shown in lines 1-3 of Table 2.

By the H-R-R Test the group of 150 subjects having red-green deficiency was separated into 89 deutans, 56 protans, and 5 who could not be classified as to type of defect because they failed only plates of the screening series. The 89 subjects who were classified as deutans included 86 who were similarly classified by the anomaloscope and the 3 who were not classified as to type by this instrument. The 56 subjects who were classified as protans by the H-R-R Test were all similarly classified by the anomaloscope. The record on the battery of tests of the five subjects who were not classified as to type by the H-R-R Test is shown in lines 4-8 of Table 2.

Thus, with the exception of three subjects who were classified by the H-H-R Test but not by the anomaloscope, and of five subjects who were classified by the anomaloscope but not by the H-R-R Test, the separation into deutan and protan

For 40 subjects whose color vision was shown to be normal by our battery of tests, the average match point (computed as the center of the match range) occurred at 39.6 on the scale; the individual match points varied from 34 to 46 (cf. Trendelenburg's average normal match of 40; range for normals, 35 to 47.5). The match range with the eyes unfatigued never exceeded 4 scale divisions, in all but 5 cases being 1 to 2 scale divisions.

types by the two tests is the same. There were no conflicts in classification as to type of red-green defect by the two methods. We feel confident, therefore, that the critical hues and values used in our plates are correct for the separation of the deutan and protan types of red-green vision.

Test-Retest Reliability of the H-R-R Plates as a Device to Classify Type of Defect (Qualitative Diagnosis): As previously stated, in 238 cases the H-R-R Test was administered twice. Of these, 131 subjects showed normal and 107 defective red-green vision on the first trial and 132 showed normal and 106 defective red-

TABLE 2.—*Record on Battery of Tests of Subjects Who Were Unclassified as to Type of Red-Green Defect by the Nagel Anomaloscope (Subjects 1-3) and by the H-R-R Plates (Subjects 4-8)*

		Anomaloscope		Ishihara					
Subject	H-R-R	Match Range	Diagnosis	Errors	Diagnosis	A. O. Errors	Navy Lantern	Color Threshold Tester Score*	Dichotomous
1	Mild deutan	35-45	Uncl.	8	Deutan	14	Passed	56	Passed
2	Medium deutan	20-57	Uncl.	11	Deutan	17	Failed	28	Deutan
3	Medium deutan	15-65	Uncl.	12	Deutan	16	Failed	20	Deutan
4	Mild, Uncl.	16-18	Deutan	6	Uncl.	9	Passed	57	Passed
5	Mild, Uncl.	26-36	Deutan	4	Deutan	6	Failed	55	Passed
6	Mild, Uncl.	25-35	Deutan	4	Uncl.	6	Passed	63	Passed
7	Mild, Uncl.	20-28	Deutan	3	Uncl.	5	Passed	56	Passed
8	Mild, Uncl.	62-66	Protan	5	Uncl.	10	Passed	60	Passed

* Several interpretations of score on this test have been suggested. A score of 50 or more is now being used by the Air Forces to qualify a subject as color-defective safe; a score or less than 50, to rate him as unsafe.

TABLE 3.—*Test-Retest Results* on the H-R-R Plates as a Device to Classify Type of Red-Green Defect (Qualitative Diagnosis)*

		Retest →				
			Defective			
		Normal	Uncl.	Deutan	Protan	Test Totals
Test ↓	Normal	**130**	*1*	..	..	131
Defective	Uncl.	*2*	**2**	..	..	4
	Deutan	...	..	**59**	..	59
	Protan	...	*1*	..	**43**	44
	Retest totals	132	4	59	43	238

* Normal = no errors on Plates 3-5; unclassified, one or more errors on Plates 3-5 and none on Plates 6-14; deutan, failing more G and RP than R and BG designs on Plates 6-14; protan, failing more R and BG than G and RP designs on Plates 6-14.

green vision on the second trial (Table 1). In Table 3 the test-retest results are further subdivided to show the type of red-green vision found on each trial: normal, defective but unclassified as to type, deutan, and protan. Figures in boldface type show the number of subjects who fall into the same category as to type of defect on test and retest; figures in lightface italic type show the number who shifted category on the retest. It is seen in this Table that for only 1 of the 103 subjects (1%) who were classified as to type of red-green defect on the first test was the qualitative diagnosis changed on the retest—from protan to unclassified. Since this subject showed a protan type of defect on the anomaloscope, the first trial may be considered to have given the correct diagnosis.

The strong agreement between the classifications as to deutan and protan type on test and retest proves that the H-R-R Test has very high reliability for making this qualitative diagnosis.

3. *The H-R-R Plates as a Device to Indicate Extent of Defect (Quantitative Diagnosis).*—This aspect of the H-R-R Plates is new in testing color vision by means of a practical, simply administered test, such as is provided by properly designed pseudoisochromatic plates. Until now no printed plate test available in America has attempted it. Therefore, for this evaluation we have no single test using surface colors and giving retinal images of medium intensity and large (parafoveal) area against which to compare the quantitative estimates given by our procedure.

However, it is apparent that this feature of the test should have important applications. It is well established that even a mild degree of red-green defect results in failure to pass many of the plates of such screening tests as the A. O., Ishihara, and Boström-Kugelberg. This is the case even though the defect may not be sufficiently marked to handicap the subject in making the color judgments required in many occupations. At a recent meeting of the Armed Forces-NRC Subcommittee on Color Vision it was recommended that analysis with respect to color vision requirements be made in the various occupational specialties in the Navy and that in this connection color tests be studied which yield a quantitative score rather than merely a pass-fail score. To meet this requirement it would be necessary to administer tests of graded degrees of difficulty. Merely to increase the number of tests of approximately the same order of difficulty does not offer a solution.

In our opinion it is important to carry out such a program in relation to vocational selection and guidance in general; that is, it is important that an analysis be made with respect to the severity of the color vision requirements of various occupations and that color tests which yield a quantitative as well as a qualitative diagnosis be correlated with these color vision requirements. Textile workers, color inspectors, dye matchers, etc., should unquestionably be required to have normal color vision. On the other hand, those whose task is merely to identify by name or to recognize colors of medium and high chroma may be able to perform their tasks satisfactorily if their color anomaly is only of mild degree. We feel that the H-R-R Plates offer in a single test a long step toward the achievement of this aspect of vocational selection and guidance. An example of the usefulness of the H-R-R Test as applied to the radio and television industry will be given in a report now in preparation.

The principle used in the H-R-R Plates for the quantitative diagnosis is to present designs of each critical hue in increasing steps of chroma from low to as high as could be obtained in suitable pigments, keeping values properly adjusted, and in general to rate the extent of defect in terms of the highest chroma of design failed. This procedure is based on the assumption that the hues which are critical for the dichromatic subject of each type (i. e., the hues he matches to neutral gray) will be hues to which the anomalous trichromat of each type has reduced sensitivity. We believe our results on both the qualitative and the quantitative aspects of the test show that this assumption is valid.

A number of plates having designs in graded steps of chroma were available to us in a preliminary survey of 110 subjects shown by our battery of tests to have normal red-green vision and 57 subjects shown by this battery to have defective

red-green vision. The plates having designs of very low chroma (Plates 3-5) used for screening were selected on the criterion that all should be passed by those whose red-green vision is normal, but that one or more should be failed by those whose red-green vision is defective. The remaining plates were assembled into three additional series for the quantitative diagnosis: Plates 6-9, having designs of low chroma, to be used to indicate mild red-green defect when one or more are failed and the remaining Plates 10-14 are passed; Plates 10-12, having designs of moderate chroma, to be used to indicate medium red-green defect when one or more are failed and the remaining Plates 13-14 are passed, and Plates 13 and 14, having designs of the highest available chroma, to be used to indicate strong red-green defect when one or both are failed. At the present time we feel that a threefold category of extent of defect (mild; medium; strong) is the largest practicable in the test situation.

Several criteria guided us in making the tentative selection of the plates which were to comprise the three series for the quantitative diagnosis: (*a*) the chromas used in the designs on the plates; (*b*) the percentage of color-defective subjects failing each plate as indicative of the relative difficulty of the different plates; (*c*) the usefulness of each plate for the qualitative diagnosis whatever the extent of defect, and (*d*) the performance of each subject on other tests of the battery.

Within each of the three series of plates for the quantitative diagnosis, there is some gradation in chroma, a feature which is necessary to insure the qualitative diagnosis in all cases; further, we recognize that there must be gradations of defect within each of the three groups we have perhaps arbitrarily established. That is, on the H-R-R Test a subject will be rated as having a medium defect whether he fails only one or all three of Plates 10-12, so long as he correctly recognizes all designs on Plates 13 and 14. However, the subject who fails only one plate of this series is probably more nearly borderline between mild and medium in extent of defect than is the subject who fails all three plates. It should be pointed out that when there is only one failure in Plates 10-12, this failure may occur on any one of the three plates of this series.

Later work may show that a better assembly of the plates can be made for the indication of mild, medium, and strong defect, or that intermediate classifications may have practical value, e. g., mild-medium, or medium-strong. However, with the assembly previously noted and shown in the record sheet (Chart 1), our preliminary survey, based on 57 subjects with defective red-green vision, rated 22.8% as having mild defect, 29.8% as having medium defect, and 47.4% as having strong defect.

We have since administered the test as set up in the preliminary survey to approximately 500 more subjects with normal red-green vision by our criteria and to 93 more subjects with defective red-green vision, and have found no reason for altering the original assembly of the plates into the three series for the quantitative diagnosis. Of the total 150 subjects with defective red-green vision considered in this report, 22.7% were rated as having mild defect, 30.7% as having medium defect, and 46.7% as having strong defect. There is a rather remarkable agreement as to the distribution of extent of defect in the smaller and larger groups studied. At intervals during the accumulation of cases, we had occasion to compute similar percentages. This was done after records on 94 and 119 subjects had been completed. In Table 4 are shown for comparison the percentages of subjects rated as

having mild, medium, and strong defects when the cases studied numbered 57, 94, 119, and 150. A comparison of the first with the last column indicates that no matter how far the number of subjects studied should be extended the percentages would remain very nearly the same.

The relative difficulty of the individual plates is shown in Table 5. In this Table the percentage of 150 subjects with defective red-green vision who fail each of Plates 3-14 is given. The notation (G) in connection with the plate number indicates that green and blue-green designs are paired on the plate; the notation (R) indicates that red and red-purple designs are paired.

A very large proportion of the subjects fail to see either the colored designs of very low chroma that comprise the screening series or those designs of low chroma that make up the mild series (Plates 3-9). Approximately 60% of the group fail

TABLE 4.—*Percentage of Subjects* Having Defective Red-Green Vision Rated by the H-R-R Plates as Having Mild, Medium, and Strong Defect*

Extent of Defect	N = 57, %	N = 94, %	N = 119, %	N = 150, %
Mild	22.8	24.5	24.4	22.7
Medium	29.8	26.6	29.4	30.7
Strong	47.4	48.9	46.2	46.7

* These percentages were computed after 57, 94, 119, and 150 subjects had been studied.

TABLE 5.—*Relative Difficulty of Each Plate 3-14 of the H-R-R Test as Indicated by the Percentage of 150 Subjects with Defective Red-Green Vision Who Fail Each Plate**

H-R-R Test	Plate No.	Percentage Failing, %	H-R-R Test	Plate No.	Percentage Failing, %
Screening series (Plates 3-5)	3 (R)	90	Medium series (Plates 10-12)	10 (R)	71
	4 (R)	89		11 (R)	62
	5 (G)	98		12 (G)	51
Mild series (Plates 6-9)	6 (G)	95	Strong series (Plates 13-14)	13 (R)	45
	7 (R)	80		14 (R)	44
	8 (G)	89			
	9 (G)	84			

* The notation (G) in connection with the plate number indicates that green and blue-green designs are paired on the plate; (R), that red and red-purple designs are paired.

the plates included in the medium series, in which the chroma of the designs has been increased to a moderate degree (Plates 10-12). The designs on the plates of the strong series are of the highest chroma available and are failed by slightly less than half the subjects with defective red-green vision. Thus we are able to divide the subjects with defective red-green vision into groups depending on the highest chroma of design failed as indicative of the extent of reduced red-green sensitivity.

In the report now in preparation a comparison will be presented of the ratings made for the subjects with defective red-green vision by the H-R-R Plates with their performance on other color tests of our battery. It will be shown that many of these subjects, particularly those rated as mild in extent of defect by the H-R-R Test, are capable of performing certain color tasks and therefore should not be arbitrarily barred from all vocations in which the mere recognition of surface colors is required.

Test-Retest Reliability of the H-R-R Plates as a Device to Indicate Extent of Defect (Quantitative Diagnosis): In Table 6 are given the test-retest results on the 238 subjects who were tested twice, subdivided in this Table to show the extent of defect indicated by each trial. Figures in boldface type show the number of subjects who fall into the same category as to extent of defect on test and retest. While the reliability of the H-R-R Plates for making the quantitative diagnosis, as shown in this Table, is good (93% of all subjects retesting in the same category, and 86% of the subjects with defective red-green vision retesting in the same category as to extent of defect), it is not as high as was shown in the use of the test for purposes of screening and qualitative diagnosis (Tables 1 and 3). The major shifts in the quantitative diagnosis on retest occur in the group of subjects who showed a medium extent of defect in the first trial, one of them showing a strong defect on retest and 11 a mild defect.

Study of the record of the 11 subjects who retested as mild reveals that in each case only one plate of the medium group had been failed in the first test. These cases, then, are probably borderline between medium and mild in extent of defect.

TABLE 6.—*Test-Retest Results* on the H-R-R Plates as a Device to Indicate Extent of Red-Green Defect (Quantitative Diagnosis)*

		Retest →				
			Defective			
		Normal	Mild	Medium	Strong	Test Totals
Test ↓	Normal	**130**	*1*	..	..	131
Defective	Mild	*2*	**21**	..	..	23
Defective	Medium	...	*11*	**24**	*1*	36
Defective	Strong	...	..	*2*	**46**	48
	Retest totals	132	33	26	47	238

* Normal = no errors on Plates 3-5; mild, errors on Plates 3-9, none on Plates 10-14; medium, errors on Plates 3-12, none on Plates 13-14; strong, errors on Plates 3-14.

In five of these cases the initial failure was on Plate 10; in three cases, on Plate 11, and in three cases, on Plate 12. (It should be mentioned that six other subjects who failed only one plate of the medium group did not retest as mild.) In 8 of these 11 subjects the record on the battery of tests indicates that the first test gave the truer estimate of extent of the defect. The record on this battery for the remaining three subjects is inconsistent, showing a passing score on certain of the more stringent tests and a failing score on less stringent tests.

As is seen in Table 6, the majority of subjects who did not retest in the same group of extent of defect made a better score on the retest. We are inclined to attribute this, at least in part, to a fault in the arrangement of the symbols employed in the small edition of the H-R-R Test on which this report is based. That is, in this edition the paired symbols are always oriented obliquely. An alert subject who has at times been able to recognize both symbols during the first test may suspect that when he clearly sees only one design there is probably another oblique to this. He may, therefore, search in this quadrant for minor clues, such as might be afforded by faulty registration, to aid him in detecting a design he had not seen when first tested. This fault will be rectified in the new edition of the H-R-R Plates, now in production, by orienting the paired designs in any two of the four quadrants of the plate and by introducing several plates which carry only one design.

SUMMARY

The H-R-R Polychromatic Plates offer in a single test, requiring three minutes or less for administration, a device (*a*) for screening subjects with defective color vision from those with normal color vision; (*b*) for classifying the type of defect in subjects with defective red-green and defective blue-yellow vision, and (*c*) for estimating the extent of the defect into three classes: mild, medium, and strong. The test is designed to yield no clues for memorization or coaching. The symbols are simple geometrical designs which are familiar to foreigners, illiterates, and children. The only auxiliary equipment is the proper illuminant.

As a screening device for red-green vision, the H-R-R Test is in complete agreement with the A. O. Test (Revised Selection), approved by the ISCC Subcommittee on Color Blindness, in separating out from a group of 780 subjects, 150 who showed red-green deficiency. Validation of 100% was achieved here.

As a device to classify subjects with defective red-green vision into deutan and protan types, the H-R-R Test is about as successful as the Nagel anomaloscope (the H-R-R Test being successful in 97% of the 150 subjects and the anomaloscope in 98%). There were no conflicts in classification by the two tests.

A rating as to extent of defect by the H-R-R Plates showed 22.7% of the group of subjects with defective red-green vision to have a mild defect, 30.7% to have a medium defect, and 46.7% to have a strong defect. The distribution of extent of defect remained very nearly the same as the number of subjects studied was increased from 57 to 150.

The test has high reliability as a screening device and as a device for qualitative and quantitative diagnosis. In the few cases of change of quantitative classification on retest, the original classification has usually been the more consistent with performance on other tests of our battery.

The practical importance of a comprehensive test, such as is provided by the H-R-R Plates, to vocational selection and guidance is discussed. The test is easily administered, and the information it furnishes as to type and extent of color anomaly has practical application in many fields.

REFERENCES

1. Judd, D. B.: Standard Response Functions for Protanopic and Deuteranopic Vision, J. Optic. Soc. America **35**:199-221 (March) 1945.

2. Hardy, L. H.: Standard Illuminants in Relation to Color-Testing Procedures, Arch. Ophth. **34**:278-282 (Oct.) 1945.

3. Farnsworth, D., and Kimble, P. F.: Abridgment and Administration of the A. O. 1st Edition Pseudo-Isochomatic Plates: Compilation of Research on, U. S. Naval Submarine Base, New London, Conn., Medical Research Laboratory, Color Vision Report 14, BuMed Project X-749 (Av-384-k), Dec. 9, 1946.

4. Hardy, L. H.; Rand, G., and Rittler, M. C.: A Screening Test for Defective Red-Green Vision: Test Based on 18 Pseudoisochromatic Plates from the American Optical Company's Compilation, Arch. Ophth. **38**:442-449 (Oct.) 1947.

5. Hardy, L. H.; Rand, G., and Rittler, M. C.: Tests for Detection and Analysis of Color Blindness: I. An Evaluation of the Ishihara Test, Arch. Ophth. **34**:295-302 (Oct.) 1945.

6. Trendelenburg, W.. Über die für das Anomaloskop geeignetste Lichtqualität sowie über die Frage der Übergangsfälle zwischen Norm und Protanomalie, Klin. Monatsbl. Augenh. **102**:769-788 (June) 1939.

OCULAR MANIFESTATIONS OF INFECTIOUS MONONUCLEOSIS

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INFECTIOUS mononucleosis has become of increasing importance, particularly since the introduction of the heterophile agglutination test in 1932. The establishment of the pathologic picture of infectious mononucleosis has awakened the medical profession to the numerous problems associated with the disease. Among these are its high incidence rate, prolonged disability, and the multiple and varied manifestations of involvement of nearly every organ system of the body. Some results are permanent; death may occur.

To the present time there has been little recognition of the disease by ophthalmologists. Accounts in the American ophthalmological literature regarding any of the multiple manifestations which concern the eye apparently are confined to one report [1] of bilateral papilloretinal edema. Patients recently seen with ocular involvement of infectious mononucleosis stimulated this study.

Infectious mononucleosis is an acute, usually self-limited infectious disease of unknown etiology, characterized more commonly by fever, lymphadenopathy, acute respiratory tract symptoms, and the presence of atypical lymphocytes and of heterophile antibodies in the circulating blood. Usually it is emphasized as a children's disease, but our increasing ability to diagnose accurately has revealed its frequent occurrence in older patients.[2] There is some evidence * of an actual increase in occurrence of the disease. It is one of the acute diseases of the widespread reticuloendothelial system, almost certainly infectious in nature. So far, experiments in transmission of the disease to both animals and man have given conflicting results. The presumption of a filterable virus as the causative agent is widely accepted, but the etiologic agent has not yet been identified.

HISTORY

Our knowledge of the disease stems from the first clinical description in the literature, credited to Filatov,[6] in 1885, who termed it "idiopathic lymphadenitis." In 1889 Pfeiffer [7] gave a more comprehensive clinical description, entitled "Drüsenfieber." This first period of clinical description was closed abruptly in 1920 by the discovery of the blood changes in the disease. The classic description of the hematology of infectious mononucleosis was published by Downey and McKinlay [8] in 1923. This period, dominated by the hematologists, lasted until 1932, when the serologic period opened with the dramatic discovery of the Paul-Bunnell [9] test for anti-sheep-cell agglutinins

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* References 3, 4, and 5.

in the serum of patients with the disease. The fourth period is that of description of the pathology. We now know that infectious mononucleosis is a generalized disease, and that there is a typical lesion with infiltrations of normal and abnormal lymphocytes in almost every organ of the body.

PATHOLOGY

The development of a clear picture of the pathology of infectious mononucleosis has been largely due to the work and publications of Ziegler,[10] Allen and Kellner,[11] and Custer and Smith.† These are based upon a total of 10 autopsies, prior to which pathologic study was confined to surgical and biopsy specimens.

The basic lesion is a perivascular infiltration of both normal and abnormal lymphocytes, found by Custer and Smith [12] in all the tissues they studied except bone marrow. They believe these cells to be metaplastic and to be formed in situ from other cells of the reticuloendothelial system. The cells are not considered invasive.

This fundamental and characteristic lesion is not at all uniform in its distribution throughout the body, and in any individual patient may be most marked in the central nervous system, liver, lungs, or other organs or systems. These lesions may persist long after the patient is considered to be well.[11] Lesions of the special sense organs are somewhat rare, but it is likely that hitherto they have been overlooked. There are few reports of eye lesions or manifestations. As far as is known, there have been no histologic studies upon the eye in infectious mononucleosis.

DIAGNOSIS

The clinical manifestations of infectious mononucleosis are variable in nature and severity, and it may simulate many other diseases. Hepatitis, cardiac involvement, unusual splenic enlargement, nephritis, skin eruptions, and central nervous system involvement are frequently reported. Ocular lesions are undoubtedly commoner than our literature would indicate.

The diagnosis of infectious mononucleosis is difficult due to this variable involvement and symptomatology. The disease is infrequently correctly diagnosed without the aid of the recognition of the abnormal lymphocytes in the blood stream and the presence of a high titer of sheep cell agglutinins in the serum. The heterophile agglutination test is positive at some time in the disease in from 80 to 85% of cases.[14] The test has recently been made more nearly specific by the differential absorption of these heterophile antibodies.[14] The abnormal lymphocytes, however, are not specific for infectious mononucleosis only, as they are seen in other virus diseases.[15] In most instances these cells comprise a high percentage of the total white cell count.[2]

OCULAR MANIFESTATIONS

The ocular manifestations may well be divided into two groups:

1. Those possibly due to direct involvement of the eye and its adnexa by the characteristic pathologic lesion of infectious mononucleosis.
2. Those affecting vision and the neuro-ophthalmologic apparatus apparently owing to a more remote occurrence of the lesion, most commonly involving the central nervous system.

† References 12 and 13.

The first group may include conjunctivitis, eyelid and periorbital edema, episcleritis, uveitis, optic neuritis, papilledema, retinal edema, and retinal hemorrhages. The second group includes extraocular muscle paralyses, ptosis, nystagmus, disturbances of conjugate deviation, hemianopsia, scotomata, and hippus.

During the usual course of infectious mononucleosis, conjunctival suffusion is not unusual. Numerous reports in the literature include conjunctivitis as a part of the disease.‡ Some consider it to be of diagnostic importance,[22] or specific in type.[23] It may be a presenting sign or precede the fever, and is often of a dry granular character,§ frequently unilateral,[25] and oftener on the left side. The incidence of conjunctivitis varies from a very few,[26] in a large series of cases, to as high as 40%, in some smaller series.[27]

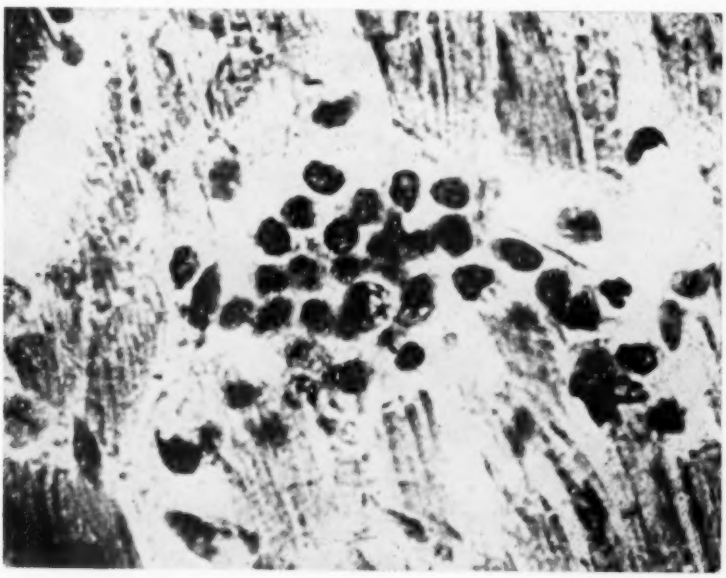

Fig. 1 (Custer and Smith [12]).—Heart. Focus of normal and atypical lymphocytes in the interstices of the heart; in most instances such collections are perivascular in position. Slight edema is occasionally noted, but muscle fibers show no structural changes. × 800.

The palpebral conjunctiva may be fiery red with discrete, punctate, whitish follicles. Most authors consider the conjunctivitis in infectious mononucleosis to be an infection of the lymphatic system.[28] Membranous conjunctivitis occasionally occurs, and Falkenberg [29] reports two cases treated for diphtheritic conjunctivitis before the true nature of the disease was discovered through the laboratory tests. No reports of cytologic study or of biopsy of the conjunctiva in this disease were found.

Periorbital edema || and puffiness of the eyelids is not uncommon and may be as striking as that seen in trichinosis.[30] Episcleritis [38] and uveitis [33] were noted in the literature only once, without description of the eye. Four other instances of non-

‡ References 16, 17, 18, 19, 20, and 21.

§ References 22 and 24.

|| References 4, 5, 16, 17, 28, 30, 31, 32, 33, 34, 35, 36, and 37.

granulomatous uveitis appearing toward the end of the clinical symptoms of infectious mononucleosis have been reported to me by personal communication from Dr. Hogan [39] and Dr. Thygeson.[40]

Pain on rotating the eyes is not an unusual symptom, and deep orbital pain, headache, and photophobia are common symptoms.

The earliest report including significant ophthalmoscopic findings was that of Clemens,[35] who described his study of an epidemic of glandular fever in an orphanage in 1907. Incidentally, he reported the first blood cell counts in this disease, which showed "a slight leukocytosis." All his patients had an ophthalmoscopic examination, and some abnormality of the ocular fundus was noted in over one-half of the patients.

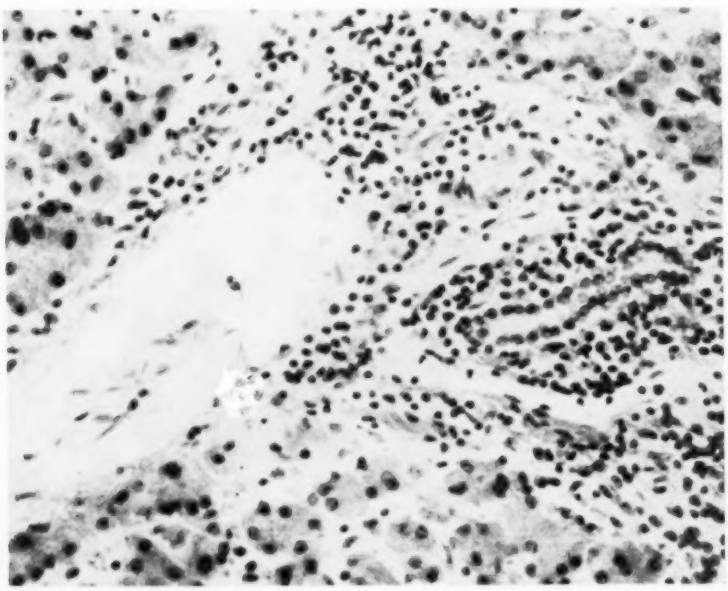

Fig. 2 (Custer and Smith [12]).—Liver. Minimal lymphocytic infiltrations of the periportal connective tissue. × 200.

These findings were called "optic neuritis" or "hyperemia of the discs," but a detailed description was not given.

Ashworth and Motto [36] noted bilateral papilledema in a patient with infectious mononucleosis, and their report, in 1947, was the first to detail this finding in the absence of a clinical picture of meningitis or encephalitis. Gsell,[41] in 1937, reported on a patient with central nervous system involvement who developed "optic neuritis" on the 10th day, the eye condition disappearing after one month. In 1948 Karpe and Wising [42] gave an excellent detailed account of a patient with infectious mononucleosis whose outstanding symptoms and signs included acute loss of vision due to severe retinal edema and, later, swelling of the optic papilla and papillitis. By the sixth day a 7 D. swelling of the retina in the macular area was present, associated with a large, dense central scotoma. The initial ocular diagnosis was that of retinal detachment, but the subsequent course led to complete recovery of vision. Exten-

sive pigmentary changes remained in the macular area. These authors concluded that the pathologic process was a part of the "neurotropism" ascribed to infectious mononucleosis, as well as its affinity for the lymphatic organs.

In 1950 well-documented reports by Blaustein [1] and Piel, Thelander, and Shaw [48] described bilateral papilloretinal edema. Piel's patient also had diplopia, a cut in the peripheral visual field, and retinal hemorrhages. Other case reports have added the observations of optic neuritis and [44] optic nerve edema, swelling, or hyperemia.¶ It is not known how often papilledema occurs in infectious mononucleosis, for routine ophthalmoscopic examinations have not been made.

Concerning the involvement of the central nervous system in infectious mononucleosis, it is apparent that transient ocular signs and symptoms are common.[49] Head-

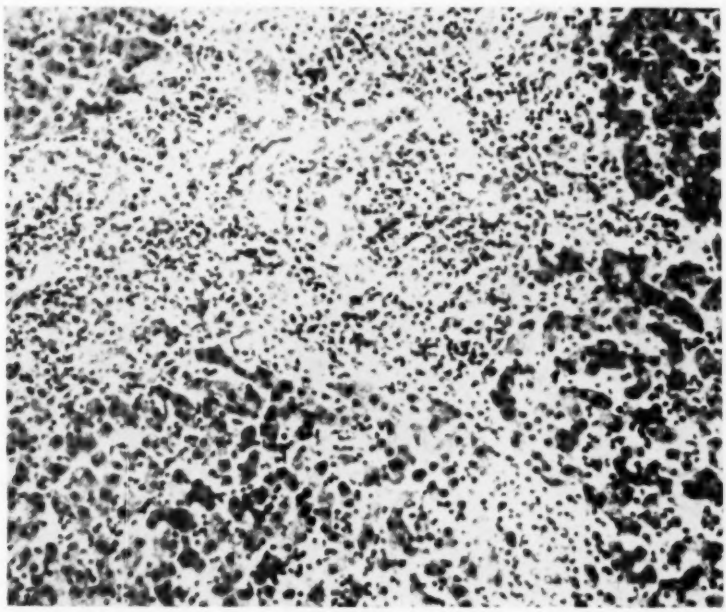

Fig. 3 (Custer and Smith [12]).—Liver. Marked periportal lymphocytosis, maximal in our series, simulating lymphoid leukemia. Lymphocytes are also conspicuous in surrounding sinusoids. × 125.

ache and blurring of vision # are considered to be among the most frequent general symptoms in this group. Bernstein and Wolff,[51] in reviewing the literature up to 1950, listed only 34 patients whose cases they considered as adequately reported and concluded that the incidence of central nervous system involvement is not over 1%. Of the 34 satisfying their requirements, however, 15 had some definite ocular manifestation. Authors with apparently less severe criteria have given a much higher incidence of central nervous system involvement in this disease. Thomsen [52] indicated an incidence of 9%, and in cases specifically studied for central nervous system involvement he found such in 23%.

¶ References 45, 46, 47, and 48.

References 18, 49, and 50.

The most frequent specific manifestation in the eye of central nervous system involvement by infectious mononucleosis is disturbance of the oculorotary apparatus. Fledelius [52] reported an isolated inferior rectus paresis in 1935. Since then there have been several reports of paralyses involving the oculomotor or other cranial nerves.* Several authors † have reported ptosis, and many have reported diplopia.‡ Dolgopol and Husson [32] reported a fatal case, clinically noted to have diplopia, in which autopsy showed a selective degeneration of the nerve cells of the nuclei of the third and fourth cranial nerves.

Nystagmus has been mentioned in several instances of infectious mononucleosis involving the central nervous system,§ and disturbances of conjugate deviation have been noted.‖

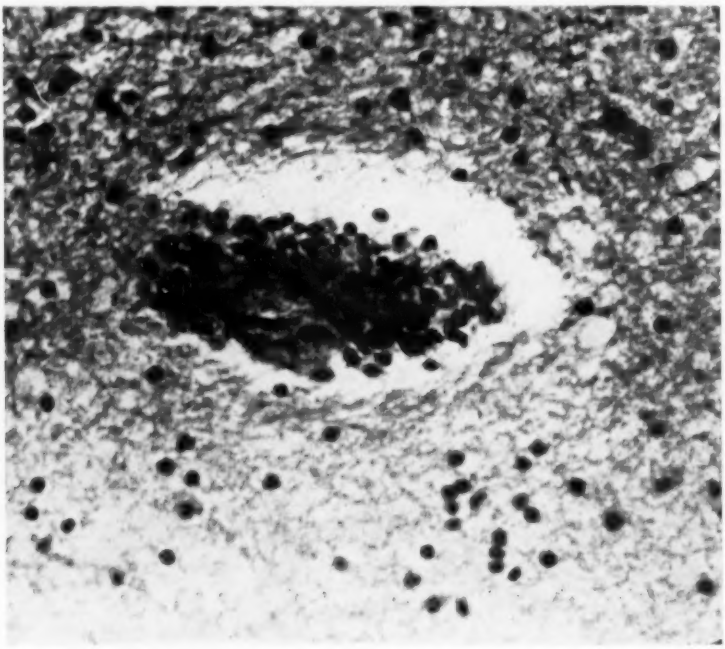

Fig. 4 (Custer and Smith [12]).—Brain. Perivascular "cuffing" and edema resembling that seen in various virus encephalitides. × 450.

Occasional reports have included merely a mention of blurring of vision,¶ visual disturbances,[33] scotomas,[33] hippus,[58] "dissociated movements of the eyes,"[51] "fluctuating pupillary size,"[51] and other vague ocular signs or symptoms.[65]

* References 47, 54, and 55.

† References 37, 38, 56, 57, 58, and 59.

‡ References 32, 33, 37, 43, 48, 60, and 61.

§ References 31, 38, 54, 57, 62, 63, and 64.

‖ References 31, 58, 59, and 62.

¶ References 33, 47, 56, 62, and 64.

CASE REPORT

Miss D. T., a 17-year-old student, first noted sudden onset of chills, fever and redness of eyes on Nov. 5, 1947. The following day she developed severe headache, general malaise, and photophobia.

On the third day of the disease, nausea and vomiting became severe, and the patient was toxic and seriously ill. She was then admitted to the hospital.

The family history and past history were not contributory.

Physical examination on entry to the hospital revealed a well-developed, obese girl who was acutely ill. The temperature was 101.8 F., pulse 70, respiration 22, and blood pressure 100/64. There was a fine, mottled papular rash over the lower abdomen and thighs. The eyes were particularly noticeable, due to intense injection of the conjunctival and episcleral vessels, associated with excessive lacrimation, intense photophobia, but no evidence of conjunctival discharge. No hypertrophy of the conjunctival follicles was present. The pupils were equal and active reflexly to light and in accommodation. Ocular media appeared clear.

The ocular fundi revealed a low degree of edema of both optic discs, slightly greater in the right eye, and accompanied by increased tortuosity of the retinal arteries and veins but no hemorrhages or exudates. The preauricular glands were extremely enlarged and tender. Slight lymphadenopathy in the axillary and submaxillary areas was present. There were no signs of an acute upper respiratory infection. The remainder of the physical examination was normal, including gross neurological examination.

On the fourth day of the disease the temperature reached 102 F. Vomiting was more forceful, and there was slight stiffness of the neck. Headache and ocular symptoms were unrelieved by local and general treatment. Circumcorneal injection was then present; the globes were tender on rotation or palpation, and there was deep orbital and ocular pain. Papilledema had progressed slightly, and elevation of the optic discs was considered to be over 1 D. The disc margins and physiological excavations were then completely blurred.

The chest x-ray was normal, and the corrected sedimentation rate was 41 mm. in one hour (Wintrobe). Lumbar puncture was considered, but was not done, owing to the heterophile agglutination test, which was found at this time to be positive in a titer of 1:2,560, and the white cell count, which was 3,900, with 30% lymphocytes, nearly all of which were of the large "foamy" type seen in infectious mononucleosis.

On the fifth day of the illness the general symptoms were markedly reduced, but the ocular signs and symptoms had increased. The papilledema was greater, as were the tortuosity and engorgement of the retinal vessels. Moderate circumcorneal injection remained. The pupillary reflexes remained acutely active. There were subjective complaints of blurred vision and marked discomfort on attempting to read.

On the sixth and seventh days of the disease the ocular signs and symptoms began to diminish with the exception of the moderate circumcorneal injection and blurring of vision. Inflammation of the uveal tract was considered, but no further objective signs could be made out on examination in the hospital. The iris and cornea appeared normal to loupe inspection.

The patient was next seen on the 13th day, and examination was first possible with the corneal microscope. Ciliary injection remained. The conjunctiva was normal. There were numerous corneal precipitates of variable size in each eye, together with a moderate aqueous ray. The precipitates were whitish in color, more conspicuously placed in the center and lower pupillary area of the cornea, and discrete in appearance. No posterior synechiae were present, and no nodules or pigmentary changes were seen in the iris. The globes remained tender, together with pain on attempted accommodation. Edema of the optic discs remained, but to a markedly slighter degree than before. Peripheral and central visual fields were normal at this time, although central visual acuity was blurred to 20/30 poorly.

Repeated instillations of 5% homatropine were adequate to dilate the pupils well and relieve the ocular tenderness and pain associated with accommodation.

Twenty days after onset of the disease there remained only equivocal evidence of the previous papilledema. Physiological excavations of the optic discs were again clearly made out.

Twenty-six days after onset of the illness there was no evidence of papilledema and the iritis appeared inactive. Many precipitates on the posterior corneal surface were still present, but most were becoming crenated and diminished in size. Central visual acuity was 20/20 in each eye.

Sixty-three days after the onset of the disease the ocular examination was normal and vision was 20/15 in each eye. The patient was entirely well.

COMMENT AND SUMMARY

A short outline of infectious mononucleosis is presented, with a review of the literature concerning involvement of the visual apparatus. The case reported is one of proved infectious mononucleosis exhibiting the previously unreported pattern of bilateral iridocyclitis and papilledema.

It is clear that there is a characteristic pathologic lesion of infectious mononucleosis. There is evidence that the potential seriousness, the high rate of incidence, and the widespread distribution of the lesion have not been fully appreciated heretofore.

Ocular involvement is commoner than the literature would indicate, as ophthalmoscopic and ocular examinations have frequently been omitted. Ocular symptoms may be among those noted in cases exhibiting prolonged courses. Reports of histologic or cytologic study of the eye or its adnexa in patients with infectious mononucleosis were not found. The possibility of this disease being a causative agent in certain cases of conjunctivitis, periorbital edema, retro-orbital pain, optic neuritis, retinal edema, and uveitis is suggested.

In the case reported the papilledema occurred in the absence of a clear clinical picture of encephalitis or meningitis, and was associated with pain on rotation of the eyes or backward pressure on the globe, together with mild visual symptoms. There is reason to believe the optic disc edema represented an optic neuritis or papillitis as an inflammatory change. The concurrence of an active anterior uveitis and pain on rotation of the globes lends weight to this observation. The iridocyclitis clinically appeared to be a nongranulomatous type. The course of the ocular manifestations was short, and there was no evidence of tissue destruction and no permanent functional loss resulted. The early presence of fever, vomiting, headache, and papilledema presented a difficult and serious diagnostic problem. The laboratory finding of a positive heterophile agglutination test in high titer and the observation of the infectious mononucleosis cells in the blood stream can be of great aid.

DISCUSSION

Dr. L. Weston Oaks, Provo, Utah: I should like to point out for a moment something that characterizes this Society. Dr. Cordes said some years ago, on one occasion, that the Pacific Coast Oto-Ophthalmological Society has a habit of bringing to its meetings more new material than any like organization. I think this meeting is no exception, and the papers we have listened to this morning have been strikingly in such a class. I am sure that if our dean of ophthalmology in the western United States, the late Edward Jackson, chief founder of this organization, might have had the opportunity to listen to the program we have had at this meeting, he would have been very happy at the results of his arduous efforts to bring about this Society.

This paper of Dr. Tanner's is important. It involved very much more material than has been presented. It required also many, many tedious hours of work, which show up in his bibliography and in his observations. Infectious mononucleosis is an important disease and, at first sight, would seem to be protean in the scope of its manifestations. It is one that I am sure is being missed frequently, partly because we are not aware of the things that have been told us this morning and partly because the general men are missing the condition. We do not see it often in this area; yet I am confident that it does occur here.

There is one view of it, recently mentioned by A. Piney, of London, in his book, "Diseases of the Blood," which I have not seen advocated elsewhere. He believes it to be a disease of the blood, and in support of it is the fact that the disease seems to affect every tissue of the body, with perhaps the exception of the bone marrow. Such being the case, it would not be difficult to explain why the passage of lymphocytes into the tissues occurs, particularly along blood vessels. There is something peculiar about the pathologic situation, in that these lymphocytes lie there such a long time before body scavengers appear able to move them. In severe cases splenomegaly and adenopathy are reported to have lasted as long as two years, after apparent termination of the disease with regard to other features. Of those complex chemical changes that occur in blood, the fluid tissue, to lower thresholds of capillary permeability, we know little. Study of plasma proteins, serum calcium-phosphate levels, and integrity of other chemical participants will perhaps cast some light upon processes involved. Pertinent investigation is needed to give us better means of controlling the inexplicably long period of convalescence.

The diagnosis is not easy from the standpoint of clinical observations. Piney has described three different types of the disease: one, the violent acute form, which has been recognized longer than any other; another, somewhat less violent, in which there is a membrane in the fauces, and a third, or chronic form, characterized only by the blood changes and by pyrexia. To confuse further the clinical picture, there is also an acute infectious lymphocytosis, believed to be of virus origin, which has all the features, over a short duration, of infectious mononucleosis without the positive blood test. Piney states that the lymphocytosis and the presence of so-called Downey cells may precede by several days the onset of clinical symptoms. Raymond Goodale, on the other hand, points out that there may actually be leucopenia during the first week of the illness. The apparent contradiction would seem to hinge upon the above-mentioned various forms of the disease.

Other diagnostic pitfalls are present, too. In the acute and severe forms, stiffness of the neck, a positive Kernig sign, turbid cerebrospinal fluid with high cell count, increased total protein, and positive Pandy test, often occur to lend complexity. Confusion with central nervous system conditions is readily excusable, because not a few of the acute cases manifest characteristic symptoms of meningitis which would lead one to such a conclusion.

Dr. Tanner mentioned the case described by Karpe and Wising, of Copenhagen, in 1948, in which there was rapid deterioration of vision due to pronounced edema in the maculae. Later there was papillitis, and, finally, return of vision to normal, with only residual pigmented spots of the retinae to testify to what had transpired. To me this observation has another interesting significance. Here is a patient who had such violent disturbance and elevation of the macular area as to make the observer suspicious of a detachment. There was, as nearly as one can tell, an absolute central scotoma in each eye. When the process had subsided, definite pigment changes were left in the retina, and yet there was no evidence, as witness the return to perfectly normal vision, that any break-through occurred in Bruch's membrane. Such an outcome is decidedly unusual.

It is likely that further observations are going to come out of this study that will give us even more definite evidence of the nature of the condition which we recognize as infectious mononucleosis. I thank Dr. Tanner for his paper and for the privilege of discussing it.

Dr. Owen C. Dickson, Berkeley, Calif.: I wish to add my congratulations to Dr. Tanner, and to agree that this is a condition which is important for us to pay a considerable amount of attention to in the future.

As Dr. Tanner mentioned, there is only one other article in the English ophthalmological literature dealing with the ocular manifestations of infectious mononucleosis. There are two articles in the *Acta ophthalmologica* which deal with ocular manifestations of infectious mononucleosis.

In going over records and statistics which were available at Cowell Memorial Hospital, the student hospital at the University of California in Berkeley, several interesting things were apparent, the first of which is demonstrated in Table I. This indicates that over the period from 1947 to 1951 hospital admissions for infectious mononucleosis rose from 143, in the school years 1947 to 1948, to 225, in the years 1950 and 1951. The total registration at the hospital during that

period of time varied from 30,230 to 27,595. Total hospital admissions rose from 3,048 to 3,241. Hospitalization for infectious mononucleosis, however, rose from 143 to 225, or over 50%. This may mean one of two things. Either infectious mononucleosis is becoming more prevalent, or the cases are becoming severe enough to require hospitalization oftener.

Table 2 shows the number with ocular complaints in patients hospitalized from January to June, 1948. Over half of the patients at one time or other had ocular signs or symptoms. Men and women were equally affected.

TABLE 1.—*Patients Hospitalized with Mononucleosis*

Year	Registration *	Hospital Admissions	Mononucleosis
1947-1948	30,230	3,048	143
1948-1949	30,864	2,926	166
1949-1950	30,705	3,200	200
1950-1951	27,595	3,241	225

* Registration = total number of persons who registered any time during fiscal year.

TABLE 2.—*Ocular Complaints in Patients Hospitalized for Mononucleosis from January to June, 1948*

	Men	Women	Total
With ocular disturbance	19	15	34
Without ocular disturbance	17	14	31
	36	29	65

TABLE 3.—*Types of Ocular Disturbance*

	Men	Women	Total
Eye pain	10	5	15
Icterus of sclerae	2	2	4
Injection of conjunctiva	4	3	7
Swollen tear gland	0	1	1
Eye burning	3	2	5
Edema	9	3	12
Eye watering	0	2	2
Photophobia	2	1	3
Eye fatigue	1	0	1
	31*	19*	50*

* Some patients had more than one ocular disturbance.

Table 3 shows a further breakdown of the types of ocular disturbances. The three commonest, in order of frequency, are pain in or behind the eyes, edema of the conjunctiva, and redness of the conjunctiva.

In this group of 65 patients there were none of the serious ocular manifestations which have been described by Dr. Tanner. A patient was seen recently for an eye examination, and, because of suspicious-looking optic discs, a central visual field determination was done. The patient was found to have a minimal field defect to 1/1000 white. She gave a history of having had infectious mononucleosis 11 years before. On checking back in records, which were again available at Cowell Memorial Hospital, we found that this young lady had been hospitalized at that time with presenting symptoms of spots before the left eye and the usual severe headache and nausea which frequently accompany the general disease. At that time she was examined by several of the doctors, and, incidentally, by Dr. Millard Gump, who is here today. There were definite edema of both discs and three or four "splinter" type hemorrhages at the upper portion of the left disc.

Vision was apparently not affected. The edema and the hemorrhage gradually cleared over the period of the next 9 or 10 days, and no further visual loss was described. This, I feel, could easily represent a mild case of the neuropathy which is caused by infectious mononucleosis.

Again, I feel that Dr. Tanner is to be commended for the thoroughness of his paper, and for the fact that he is calling it most specifically to the attention of the ophthalmologists.

DR. O. R. TANNER, Palo Alto, Calif.: I wish to thank Dr. Oaks and Dr. Dickson for being so kind to me in their discussion.

There are two points I might make at this time. I did not mention that both Custer and Smith, who have studied the pathology of this disease the most thoroughly of any, felt that these lymphocytic cells were formed from the reticuloendothelial system in situ, and that they were not invasive. This fact may have some bearing on the point that Dr. Oaks brought out in regard to the lack of extensive damage or of breaking of Bruch's membrane in the patient with retinal edema reported.

I am very happy to note that Dr. Dickson was able to go back and find the thing that I felt to be most important, i. e., that ocular disturbances were much commoner than we were able to verify in our literature and that we had not previously been paying attention to them. One wonders if ophthalmological examination of those patients elicited was done uniformly and whether it is not possible that many of those patients may have had low-grade papilledema or other signs and symptoms of ocular involvement of the disease.

Many of these patients that we have been seeing are students at Stanford University. We are seeing an increasing number of ocular manifestations, as we have organized the medical staff with the ophthalmologists in order to review each and every patient with the diagnosis. I think that probably is the only way to ferret out the important cases from those with minimal disturbances.

REFERENCES

1. Blaustein, A., and Caccavo, A.: Infectious Mononucleosis Complicated by Bilateral Papilloretinal Edema, Arch. Ophth. **43**:853 (May) 1950.

2. Sturgis, C. E.: Hematology, Ed. 1, Springfield, Ill., Charles C Thomas, Publisher, 1948, p. 640.

3. Houck, G. H.: Infectious Mononucleosis, Editorial, Am. J. Med. **7**:699 (Dec.) 1949.

4. Creaturo, N. E.; Akerson, I. B., and Flanagan, M. M.: Infectious Mononucleosis: A Report on 24 Cases, Connecticut M. J. **12**:526 (June) 1948.

5. Infectious Mononucleosis, Editorial, J. A. M. A. **134**:1548 (Aug. 30) 1947.

6. Filatov, N. F.: Lectures on the Acute Infectious Diseases of Children, Ed. 1, Moscow, A. Lang, 1885, Vol. 1, Chap. 1, p. 13.

7. Pfeiffer, E.: Drüsenfieber, Jahrb. Kinderh. **29**:257, 1889.

8. Downey, H., and McKinlay, C. A.: Acute Lymphadenosis Compared with Acute Lymphatic Leukemia: Hematologic Studies, Arch. Int. Med. **32**:82 (July) 1923.

9. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90 (Jan.) 1932.

10. Ziegler, E. E.: Infectious Mononucleosis: Report of Fatal Case with Autopsy, Arch. Path. **37**:196 (March) 1944.

11. Allen, F. H., Jr., and Kellner, A.: Infectious Mononucleosis: An Autopsy Report, Am. J. Path. **23**:463 (May) 1947.

12. Custer, R. P., and Smith, E. B.: The Pathology of Infectious Mononucleosis, Blood **3**:830 (Aug.) 1948.

13. Smith, E. B., and Custer, R. P.: Rupture of the Spleen in Infectious Mononucleosis, Blood **1**:317 (July) 1946.

14. Davidsohn, J.; Stern, K., and Kashiwagi, C.: The Differential Test for Infectious Mononucleosis, Am. J. Clin. Path. **21**:1101 (Dec.) 1951.

15. Litwins, J., and Leibowitz, S.: Abnormal Lymphocytes (Virocytes) in Virus Diseases Other Than Infectious Mononucleosis, Acta haemat. **5**:223, 1951.

16. Fowler, W. M., and Tidrick, R. T.: Unusual Manifestations of Infectious Mononucleosis, Am. J. Clin. Path. **10**:548 (Aug.) 1940.

17. Gardner, H. T., and Paul, J. R.: Infectious Mononucleosis at the New Haven Hospital, 1921-1946, Yale J. Biol. & Med. **19**:839 (May) 1947.

18. Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis with Special Reference to Cerebral Complications, Am. J. Dis. Child. **61**:1131 (June) 1941.

19. Sprunt, T. P.: Infectious Mononucleosis, Internat. Clin. **3**:92 (Sept.) 1933.

20. Glanzmann, E.: Das Lymphaemoide Drüsenfieber, Berlin, S. Karger, 1930, Pt. 25.

21. Marchal, G.; Bargeton, and Mahoudeau: Angine à monocytes avec biopsie, Sang **15**:431, 1943.

22. Guthrie, C. C., and Pessel, J. F.: An Epidemic of "Glandular Fever" in a Preparatory School for Boys, Am. J. Dis. Child. **29**:492 (April) 1925.

23. Chevallier, P., and Belski-Pasquier, G.: Sur cas d'adenolymphoideite aiguë benigne (mononucléose infectieuse) simulant la leucose aiguë: La conjonctivite specifique de la maladie, Sang **14**:546, 1940-1941.

24. Schulz, E.: Eine Epidemie von Pfeifferschen Drüsenfieber, München. med. Wchnschr. **80**:1809 (Nov. 17) 1933.

25. Becker, H. F.: Klinische Beiträge zum Drüsenfieber, München. med. Wchnschr. **78**:1594 (Sept. 18) 1931.

26. Wechsler, H. F.; Rosenblum, A. H., and Sills, I. S.: Infectious Mononucleosis: Report of an Epidemic in an Army Post, Ann. Int. Med. **25**:113 (July); 236 (Aug.) 1946.

27. Ash, H. H., and Arbogast, J. L.: Infectious Mononucleosis, J. Indiana M. A. **35**:562 (Oct.) 1942.

28. Klemola, E.: Studies of Infectious Mononucleosis, Acta med. scandinav. **127**:149, 1947.

29. Falkenberg, T.: Infectious Mononucleosis, Conjunctivitis, and Serum Sickness, Nord. med. **12**:3607 (Dec. 13) 1941.

30. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85 (Feb.) 1940.

31. Field, W. W.: Infectious Mononucleosis with Severe Central Nervous System Involvement, Am. J. Med. **4**:154 (Jan.) 1948.

32. Dolgopol, V. B., and Husson, G. S.: Infectious Mononucleosis with Neurologic Complications, Arch. Int. Med. **83**:179 (Feb.) 1949.

33. Stevens, J. E.; Bayrd, and Heck, F. J.: Infectious Mononucleosis: A Study of 210 Sporadic Cases, Am. J. Med. **11**:202 (Aug.) 1951.

34. Dameshek, W., and Grassi, M. A.: Infectious Lymphadenosis ("Mononucleosis") and Thrombocytopenic Purpura: Recovery After Splenectomy, Blood **1**:339 (July) 1946.

35. Clemens, J. R.: Report of an Epidemic of Glandular Fever, Brit. J. Child. Dis. **4**:517 (Dec.) 1907.

36. Ashworth, J., and Motto, S. A.: Infectious Mononucleosis Complicated by Bilateral Papilloretinal Edema, New England J. Med. **237**:544 (Oct. 9) 1947.

37. Schultz, E. W.; Terry, M. C.; Brice, A. T., Jr., and Gebhardt, L. P.: Bacteriological Observations in Case of Meningeal Encephalitis, Proc. Soc. Exper. Biol. & Med. **31**:1021, 1934.

38. Zohman, B. L., and Silverman, E. G.: Infectious Mononucleosis and Encephalomyelitis, Ann. Int. Med. **16**:1233 (June) 1942.

39. Hogan, M. J.: Personal communication to the author.

40. Thygeson, P.: Personal communication to the author.

41. Gsell, O.: Meningitis serosa bei Pfeifferschem Drüsenfieber. (Mononucleosis infectiosa), Deutsche med. Wchnschr. **63**:1759 (Nov. 19) 1937.

42. Karpe, G., and Wising, P.: Retinal Changes with Acute Reduction of Vision as Initial Symptoms of Infectious Mononucleosis, Acta ophth. **26**:19, 1948.

43. Piel, J. J.; Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis of the Central Nervous System with Bilateral Papilledema, J. Pediat. **37**:661 (Oct.) 1950.

44. Bonynge, T. W., and Von Hagen, K. O.: Severe Optic Neuritis in Infectious Mononucleosis: Report of a Case, J. A. M. A. **148**:933 (March 15) 1952.

45. McGreevey, J. E.: Infectious Mononucleosis: Report and Discussion of a Severe Case with Hepatitis and Jaundice, Rocky Mountain M. J. **47**:269 (April) 1950.

46. Pietzonka, H.: Meningitis serosa bei Pfeifferschem Drüsenfieber, Deutsches Arch. klin. Med. **185**:153, 1939.

47. Vaughan, S. L.; Regan, J. S., and Terplan, K.: Infectious Mononucleosis Complicated by Spontaneous Rupture of Spleen and Central Nervous System Involvement, Blood **1**:334 (July) 1946.

48. Graham, S. D.; Schwartz, W. H., and Chapman, W. L.: Infectious Neuronitis Complicating Infectious Mononucleosis, U. S. Nav. M. Bull. **49**:914 (Sept.-Oct.) 1949.

49. Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis: Report of a Case, J. A. M. A. **116**:2482 (May 31) 1941.

50. Wintrobe, M. M.: Clinical Hematology, Ed. 2, Philadelphia, Lea & Febiger, 1946, p. 804.

51. Bernstein, T. C., and Wolff, H. G.: Involvement of the Nervous System in Infectious Mononucleosis, Ann. Int. Med. **33**:1120 (Nov.) 1950.

52. Thomsen, S.: Studie over mononucleosis infectiosa; cited by Karpe and Wising.[42]

53. Fledelius, M.: Augenmuskellähmung als Komplikation der Mononucleosis infectiosa, Acta ophth. **13**:150, 1935.

54. Sucher, A., and Schwartz, E.: Lymphatic Reaction and Encephalomeningitis, Wien. klin. Wchnschr. **49**:1417 (Nov. 20) 1946.

55. Bickel, A.: Les formes nerveuses et méningées de l'angine à monocytes et de la mononucléose infectieuse, Pract. oto-rhino-laryng. **11**:79, 1949; abstracted, Excerpta Med. VI. **4**:35, 1950.

56. Epstein, S. H., and Dameshek, W.: Involvement of the Central Nervous System in a Case of Glandular Fever, New England J. Med. **205**:1238 (Dec. 24) 1931.

57. Marshall, E. A.: Infectious Mononucleosis, Am. J. Clin. Path. **9**:298 (May) 1939.

58. Geliebter, S.: Acute Infectious Mononucleosis Complicated by Encephalomyelitis, Lancet **2**:753 (Nov. 23) 1946.

59. Slade, J. de R.: Involvement of the Central Nervous System in Infectious Mononucleosis, New England J. Med. **234**:753 (June 6) 1946.

60. Hiller, R. I., and Fox, M. J.: Infectious Neuronitis Associated with Infectious Mononucleosis, Marquette M. Rev. **7**:152 (Feb.) 1943.

61. Hubler, W. L.; Bailey, A. A.; Campbell, D. C., and Matheson, D. R.: Infectious Mononucleosis with Predominantly Neurologic Manifestations: Report of a Case, Proc. Staff Meet., Mayo Clin. **26**:313 (Aug. 15) 1951.

62. Hoyne, R. M.: Involvement of the Central Nervous System in Infectious Mononucleosis: Report of a Case with Ataxia and Nystagmus, Arch. Neurol. & Psychiat. **63**:606 (April) 1950.

63. Bickel, G.; Mach, R.; della Santa, R., and Ducommun, P.: Les formes nerveuses de la mononucléose infectieuse, Schweiz. med. Wchnschr. **78**:938, 1948; abstracted, Excerpta Med. VI **3**:338 (March) 1949.

64. Solomons, B., Jr.: Infectious Mononucleosis: Some Meningeal Features, J. Roy. Navy M. Serv. **31**:178 (July) 1945.

65. Minot, G. R.: A Non-Fatal Case Simulating Acute Leukemia with Anemia and Thrombopenic Purpura, M. Clin. North America **13**:1, 1929.

STUDIES IN EXPERIMENTAL OCULAR TUBERCULOSIS

XVII. Effect of Isoniazid in the Normal, Nonimmune Rabbit

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THE CHEMOTHERAPEUTIC agents available for the use against the Mycobacterium tuberculosis have been divided into two general groups [1]: (*a*) the antibiotics and (*b*) the synthetics.

The one antibiotic with a demonstrated specific action in tuberculosis is streptomycin. The action of this agent, by itself and in conjunction with various synthetics, has been extensively studied and reported upon,* both in experimental and in clinical ocular tuberculosis. The therapeutic value of streptomycin plus an adjuvant is now clearly established.

The synthetics may be subdivided into (1) the sulfones, (2) the aminohydroxybenzoic acids, (3) the thiosemicarbazones, and (4) the pyridine-carboxylic acid derivatives. A brief summary of these various groups follows.

1. The Sulfones. The first sulfone discovered with a specific bacteriostatic or bacteriocidal action against the Myco. tuberculosis was sulfoxone sodium (Diasone; disodium formaldehyde sulfoxylate diaminodiphenylsulfone [6]). The clinical use of this agent was, however, impossible on account of its high toxicity. Various other diaminodiphenylsulfones with a specific action in tuberculosis have since been discovered, the most promising of which is thiazolsulfone (Promizole),[7] with a spectrum much the same as that of paraaminosalicylic acid and with a low toxicity.

2. The Aminohydroxybenzoic Acids. The most important member of this group is paraaminosalicylic acid (PAS), the tuberculostatic property of which was first described by Lehmann in 1946.[8] While possibly less active than other antituberculosis chemotherapeutic agents, it is relatively nontoxic and finds its greatest usefulness as an adjuvant to streptomycin, where it appears to reduce greatly the resistance to streptomycin acquired by many strains of the tubercle bacillus. It is also probable that in its bacteriocidal action it acts upon a different phase of the intermediary metabolism of the Myco. tuberculosis than does streptomycin.

3. The Thiosemicarbazones. This group of chemotherapeutic agents, the most popular of which is amithiozone (Tibione), have an apparently high potency against the Myco. tuberculosis. They have been used extensively throughout Europe.[9] Recently these compounds were the subject of an editorial review in *The Journal of the American Medical Association*.[10] Unfortunately, all compounds of this class have a high toxicity for the liver, kidney, and bone marrow and for this reason have been used sparingly, or not at all, in this country.

* References 2, 3, 4, and 5.

4. The Pyridine-Carboxylic Acid Derivatives. These are the newest additions to the antituberculosis armamentarium. In 1945, the vitamin nicotinamide was found to have an activity against the Myco. tuberculosis about equal to that of paraaminosalicylic acid.[11] Isonicotinic acid hydrazide was first synthesized by Meyer and Malley in 1912,[12] and apparently forgotten. It was resynthesized by Fox in 1952.[1] This substance and its various derivatives made available water-soluble, nontoxic agents with a high activity against the Myco. tuberculosis. The member of this group with the greatest activity, and recently in common use, is isonicotinic acid hydrazide (an isomer of nicotinic acid hydrazide), usually known as isoniazid, but also parading under various proprietary trade names. Both in vitro and in vivo it is highly active against the tubercle bacillus and has a narrow spectrum almost specifically limited to the Myco. tuberculosis.† In mice 10 mg. per kilogram per diem for 21 days or less gives complete protection and destroys all viable tubercle bacilli. Treatment with 16 mg. per kilogram per diem is effective even when therapy is started 7 to 14 days after inoculation and some mice appear moribund.[15] Control mice treated with streptomycin and PAS all succumbed. The L. D_{50} dose for mice is 200 mg. per kilogram orally and 170 mg. per kilogram intravenously. Dogs are more susceptible, showing acute toxicity (respiratory failure) on doses of 70 to 140 mg. per kilogram and chronic liver damage in doses of 10 to 20 mg. per kilogram per diem. Rabbits tolerate the drug well and are able to take 9 mg. per kilogram over long periods. Rabbits treated with this dose over a 71-day period, therapy starting the day after intravenous inoculation with virulent bovine tubercle bacilli, all survived and at the end of this period showed no radiographic evidence of pulmonary lesions. All untreated controls similarly inoculated died within 22 to 30 days. However, after cessation of therapy, all treated animals relapsed and developed active disease within 10 days.

The pharmacology of isoniazid has been adequately described.‡ Unlike streptomycin, isoniazid is as effective orally as parenterally. It is rapidly absorbed, is distributed throughout the body (including the cerebrospinal fluid) in a bacteriostatic concentration, and is excreted in the urine. A recent report,[18] in which isoniazid labeled with C^{14} in the carboxyl position was injected in normal and tuberculous guinea pigs, showed that the drug is able to penetrate into caseous material relatively quickly and is retained there in significant amounts for as long as four days. The results of clinical trials in advanced forms of tuberculosis have been highly encouraging.§ Cases resistant to streptomycin have responded dramatically. The oral dose for man is 3 to 5 mg. per kilogram per diem in divided (two to three) doses. It is of low toxicity. The chief defect of isoniazid is that many strains of the Myco. tuberculosis acquire a strong resistance to the agent. This can be readily demonstrated in vitro, and resistant strains have been recovered from patients and animals. A recent report by the Chemotherapy Trials Committee of the Medical Research Council of England [23] indicates that in man bacillary resistance develops in 11% of cases at the end of the first month, in 52% at the end of the second, and in 71% at the end of the third month.

† References 13 and 14.

‡ References 16 and 17.

§ References 19, 20, 21, and 22.

When the effect of isoniazid on tuberculosis was announced early in 1952, and its effect on various types of clinical tuberculosis was recognized, it at once became evident that this agent might well be a valuable addition to the armamentarium for the treatment of ocular tuberculosis. It was therefore desirable that its effect in ocular tuberculosis be determined, whether it was bacteriostatic only or both bacteriostatic and bacteriocidal, whether used alone it was an adequate chemotherapeutic agent or whether it had best be used in conjunction with other agents which were also active against the Myco. tuberculosis, and to what extent the development of bacillary resistance might detract from its value. Further, aside from these local therapeutic problems, the eye presented a uniquely suitable site for the evaluation of such a therapeutic agent, permitting a day-by-day exact estimate of the progression or regression of the tuberculous lesions.

There is one report in the literature on the effect of isoniazid on ocular tuberculosis. Fust, Brückner, and Studer [24] infected 17 rabbits with inoculation of bovine tubercle bacilli in the anterior chamber. Five animals were kept as untreated controls, and 12 were treated with isoniazid. Two of the controls died of generalized tuberculosis, and three survived. Four of the treated animals died, the authors attributing these deaths to a probable Herxheimer reaction. Of the eight survivors, four became blind; one animal, injected subconjunctivally, recovered from a conjunctival tuberculosis, and three recovered from tuberculosis of the iris, two with functioning eyes. There were no relapses in the survivors two and one-half months after cessation of treatment. Obviously, no conclusions can be drawn from this experiment.

It has repeatedly been shown in the previous studies of this series that two types of tuberculosis can be produced in the eye of the experimental rabbit. In the normal, nonimmune animal the introduction of a proper dose of virulent human tubercle bacilli in the anterior chamber with a short incubation period, is followed by a low-grade inflammation with hard tubercles, and thereafter by acute inflammation and softening of the tubercles. A fulminating, spreading tuberculosis, with necrosis and caseation, then develops, usually ending in rupture of the globe. In immune-allergic animals the disease, after proper inoculation of the anterior chamber, is quite different. A low-grade restrained keratouveitis develops, which runs a self-limited course of several months, after which the eye clears, with a varying amount of residual damage. Necrosis caseation or rupture of the globe rarely occurs. In fact, ocular tuberculosis in the immune-allergic rabbit has an amazing similarity to the usually recognized forms of the clinical disease.

These two types of experimental disease afford excellent tests for the efficacy of a therapeutic agent. The use of normal, nonimmune animals provides a very severe test of the bacteriostatic or bacteriocidal properties. The use of immune-allergic animals provides a much less severe test, but any therapeutic action detected in such animals should theoretically be comparable to the effect in patients, where roughly the same conditions of allergy and immunity should prevail.

In view of the already demonstrated antituberculosis action of isoniazid in this experiment on its effect in ocular tuberculosis, it was decided to subject the agent used without any adjuvant therapy to the severe test afforded by normal, nonimmune animals.

PLAN OF EXPERIMENT

This experiment was primarily undertaken to explore two clinical points: (*a*) the inhibitory action of isoniazid‖ on the development of experimental ocular tuberculosis and the duration of any demonstrated inhibition, and (*b*) the therapeutic effect of isoniazid on already established experimental ocular tuberculosis and the duration of such action. As the experiment progressed and the inhibitory and therapeutic action of this agent became manifest, a third point was investigated, (*c*) the development of bacillary resistance to the isoniazid.

These three points were all investigated in normal, nonimmune rabbits. Two almost identical experiments were run, the first (Experiment I) on adult albino rabbits and the second (Experiment II) on young pigmented rabbits. The general plan of both experiments was as follows:

A large series of normal rabbits were inoculated in the anterior chamber of one eye and the animals then divided into three groups. In the first group (I) treatment with isoniazid was begun on the day of the inoculation. In the second group (II) treatment with isoniazid was begun only after definite tuberculous lesions had developed in the inoculated eyes. The third group (III) were left untreated, as controls. Thus, a comparison of Groups I and III gave information on the inhibitory action of isoniazid, and a period of observation after treatment was terminated showed the duration of the inhibition. A comparison of Groups II and III demonstrated the therapeutic action of the agent, and the period of post-treatment observation gave the incidence of recurrences under the conditions of the experiment.

After it had been established that all Group I rabbits developed active disease after termination of treatment, these rabbits were used to investigate Point *c* (the acquisition of bacillary resistance to the drug). This was done by dividing the Group I rabbits into two subgroups, leaving one subgroup untreated while the second subgroup was retreated with a second course of isoniazid. By this means we hoped to determine whether the infecting Myco. tuberculosis in the treated subgroup was still sensitive to the isoniazid or whether it had developed a resistance to the agent after the first course of treatment. The technical details of the two experiments were as follows:

EXPERIMENT I.—On April 15, 1952, a series of 36 adult albino rabbits (Group I, 12 rabbits; Group II, 12 rabbits, and Group III, 12 rabbits) were inoculated in the anterior chamber of the left eyes with 0.1 cc. of a suspension of virulent human tubercle bacilli grown for six weeks on Jensen's modification of Lowenstein's medium. The suspension was adjusted so that there were approximately 5 organisms in each oil-immersion field. A culture was made of this suspension at the time of inoculation. Twelve of these rabbits (Group I) were treated with 10 mg. of isoniazid (Nydrazid) twice daily by subcutaneous injection, this treatment being started on the day of the ocular inoculation. By May 1 none of the inoculated eyes (Groups I, II, or III) showed any reaction, and there was no growth in the culture at the time of inoculation. It was apparent that, through some technical error, the original inoculum had been made with dead organisms. Accordingly, on May 7 the anterior chambers of the right eyes of all animals were inoculated with a fresh suspension. All the control eyes, and later all the eyes of the treated rabbits, developed satisfactory lesions, while the previously inoculated left eyes remained clear throughout the entire experiment. The reported results are therefore entirely on the right eyes.

Group I.—Owing to the above technical error, these Group I rabbits had been treated with isoniazid for three weeks prior to the inoculation of the right eyes, on May 7. Treatment was continued on these rabbits up to June 18, a period of 40 days after inoculation, when it was discontinued.

After discontinuation of treatment, these rabbits all developed tuberculous disease in the inoculated right eyes. They were then used to investigate the question of any acquired resistance (Point *c*). On July 28, when the ocular tuberculosis was well established, these rabbits were divided into two subgroups, A and B. Subgroup A rabbits were left untreated, as controls for

‖ The isoniazid used was supplied by E. R. Squibb & Sons, under the name Nydrazid.

subgroup B, and treatment was resumed on the subgroup B rabbits and continued until Nov 10, for a second period of 105 days. They were thereafter kept under observation until the termination of the experiment, on Dec. 4, a period of 25 days.

Group II.—One week after inoculation the eyes of the Group II rabbits showed early tubercles and low-grade inflammation. On May 17 (10 days after inoculation) treatment with isoniazid was begun and was continued up to July 9, a period of 53 days. These rabbits were not further treated. They were thereafter kept under observation until Dec. 4, the post-treatment period of observation being 158 days.

Group III.—Group III rabbits were left untreated throughout the course of the experiment and served as controls.

EXPERIMENT II.—The anterior chambers of the right eyes of 35 young pigmented rabbits were inoculated on May 8, 1952, with 0.1 cc. of a suspension of virulent human tubercle bacilli, as in Experiment I. Treatment with isoniazid was begun in 12 rabbits (Group I) the day of inoculation. The dosage of isoniazid was the same as in Experiment I—10 mg. twice daily by parenteral injection.

Group I.—Rabbits were treated from May 8 to June 18, a period of 40 days. Treatment was then discontinued until July 28, by which time the tuberculous disease was established in all the previously asymptomatic eyes. The rabbits were then divided into two subgroups, A and B. Subgroup A rabbits were left untreated as controls for Subgroup B. Treatment was resumed on the six Subgroup B rabbits and continued until Nov. 10, a period of 105 days. They were thereafter kept under observation until Dec. 4, a period of 25 days, when treatment was terminated.

Group II.—The rabbits all developed low-grade inflammation and tubercles in the eyes by May 20. On May 28, when the ocular disease was well established, treatment with isoniazid was begun, and continued until July 9, a period of 46 days. These rabbits were not further treated but were kept under observation until Dec. 4, a period of 150 days, when the experiment was terminated.

Group III.—Rabbits were not treated at any time and served as controls for Groups I and II.

RESULTS

A. Inhibitory Effect of Isoniazid on Development of Ocular Tuberculosis.—In Experiment I, treatment with isoniazid was begun on April 15, three weeks prior to the inoculation of the right eyes, and was continued until June 18, or 40 days after inoculation. This pretreatment and continued after-treatment resulted in complete inhibition of all evidence of ocular tuberculosis during the period of treatment and for 21 days after termination of treatment. Thereafter, on July 9, the eyes of all these pretreated animals began to show evidences of ocular tuberculosis, and within three weeks the average intensity of the disease was greater than in the untreated controls, in which the disease was then on the wane. This is shown in Chart 1.

In Experiment II (Chart 2) an almost exactly similar result was observed. In this experiment treatment was begun synchronously with inoculation. The untreated controls began to develop tuberculous disease on the eighth day, while the eyes of the treated animals remained entirely asymptomatic and free of any trace of clinical tuberculous disease. Treatment was terminated on June 18, and thereafter all eyes continued free of inflammation until July 9, again a period of three weeks. At this time the eyes of all the previously treated rabbits began to develop the usual tuberculous lesions seen in normal rabbits, and within three more weeks the intensity of the disease was higher than in the controls.

In summary of the two experiments, treatment with isoniazid, begun either prior to inoculation or at the time of inoculation, gave complete inhibition of all evidences of ocular tuberculosis for the 40-day period of treatment and for 3 weeks after

termination of treatment. Thereafter the inoculated eyes of all these previously treated rabbits developed tuberculous disease of the same type and intensity as the controls. These observations clearly indicate a bacteriostatic action for isoniazid in experimental ocular tuberculosis, rather than a bacteriocidal one.

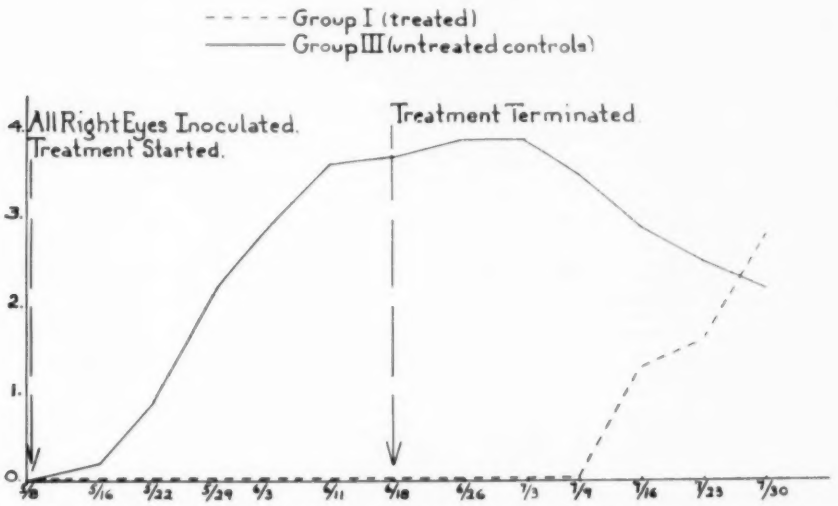

Fig. 1 (Experiment I).—Inhibitory effect of isoniazid: treatment begun prior to inoculation.

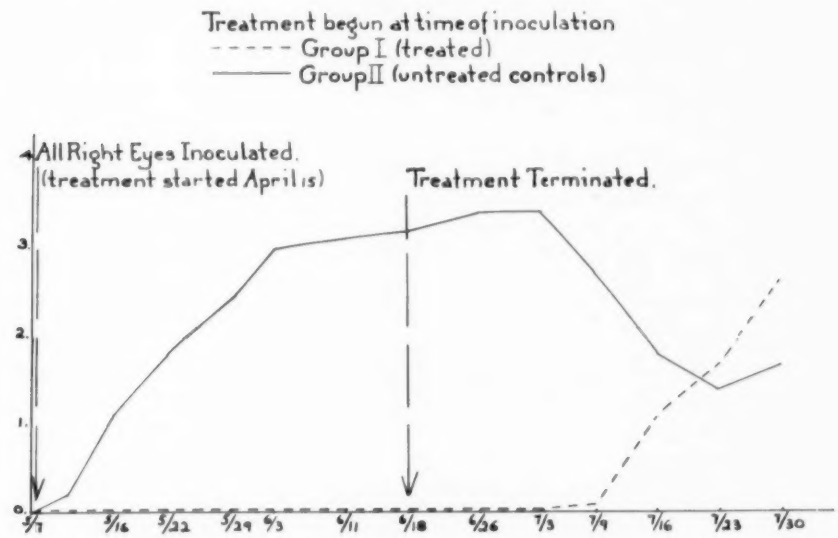

Fig. 2 (Experiment II).—Inhibitory effect of isoniazid: treatment begun at time of inoculation.

B. Therapeutic Effect of Isoniazid on Established Ocular Lesions.—The therapeutic effect of isoniazid on already established ocular lesions is shown in Chart 3 (Experiment I) and Chart 4 (Experiment II).

In Experiment I, nine days after inoculation of the right eye, all right eyes showed early, but clear-cut, tuberculous lesions. These consisted in low-grade pericorneal congestion and small hard tubercles on the cornea or the surface of the iris. Treatment was started in the Group II rabbits 10 days after inoculation. For five days there was no discernible difference between the eyes of the treated rabbits and those of the untreated controls. Thereafter there was a sharp improvement in the eyes of all treated rabbits. The tubercles regressed, and the low-grade inflammation subsided. Within one week the average activity in the treated rabbits had fallen from 1.8 to 0.6. The improvement and regression of all visible symptoms continued,

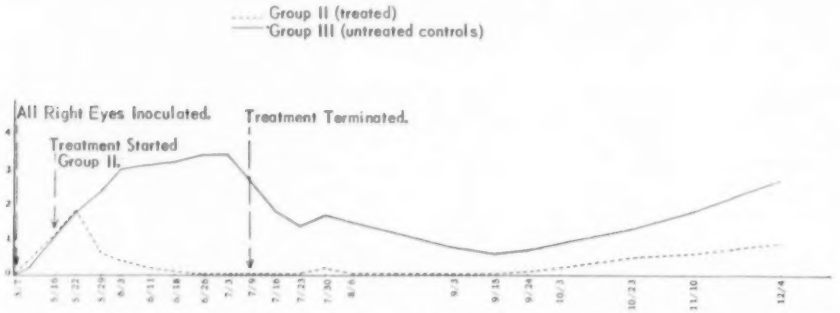

Fig. 3 (Experiment I).—Therapeutic action of isoniazid: treatment begun after development of symptoms.

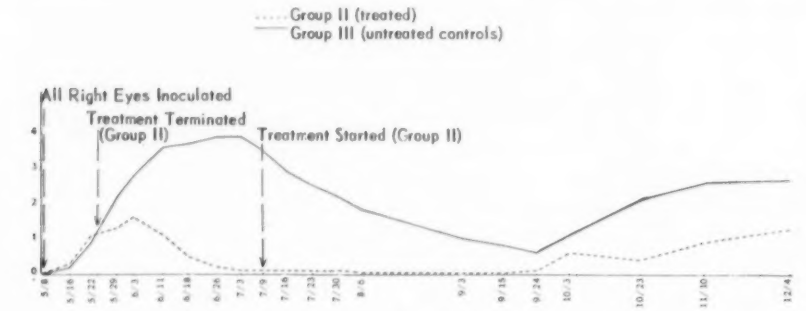

Fig. 4 (Experiment II).—Therapeutic action of isoniazid: treatment begun after development of lesions.

and by June 26, after 40 days' treatment, the eyes of all treated rabbits were free of all clinical evidence of active tuberculous disease. In the meantime the disease had increased steadily in the eyes of the untreated controls, and by June 26 over 50% of these eyes had ruptured. On July 9 there were 11 survivors in the Group II rabbits, and all of these were free of inflammation, the only evidence of previous disease being a few posterior synechiae in an occasional eye. Treatment was then discontinued. The eyes remained asymptomatic until Sept. 3, a period of 56 days, when early symptoms of ocular tuberculosis began to develop in one rabbit. In a second rabbit the infection broke through on Oct. 3 and a rapidly spreading, fulminating ocular tuberculosis developed. Three rabbits died between Sept. 26 and Oct. 22, all without recurrences at the time of death. At the conclusion of the

experiment, on Dec. 4, there were eight survivors among the Group II rabbits. Three of these had remained free of symptoms for the 150 days after termination of treatment; two had developed advanced caseous tuberculosis, and three had developed low-grade but active tuberculosis.

In summary, all 12 of the treated rabbits showed complete control of all evidences of ocular tuberculosis after 40 days of treatment with isoniazid. The first recurrence was noted 56 days after termination of treatment. Thereafter, of the eight surviving rabbits, 5, or 62%, developed recurrent ocular tuberculosis, while 3, or 38%, remained free of recurrence up to the end of the experiment, five months after termination of treatment.

In Experiment II (Chart 2) these findings were confirmed. Symptoms developed in the eyes 12 days after inoculation, and by the 20th day all eyes showed definite ocular tuberculosis. Treatment was then begun, and after 32 days the disease was completely under control in 9 of the 12 rabbits, while 3 showed a trace of residual activity. This was the picture on July 9, when treatment was terminated, after a period of 46 days. By August 16 the 3 eyes with slight activity had cleared, and activity in all 12 rabbits in this group was recorded as "zero." This complete control of the disease continued up to Sept. 24, when one recurrence was noted. Within the next two months seven other rabbits had recurrences, while four remained asymptomatic. There were no deaths in this group.

In summary, treatment with isoniazid controlled all evidences of active inflammation in the entire group. After termination of treatment, all animals remained free of symptoms for 66 days, when the first recurrence was noted. At the end of the experiment, on Dec. 4, or 126 days after termination of treatment, there had been eight recurrences, an incidence of 66%.

In summary of the two experiments, in 24 rabbits with well-established ocular tuberculosis, treatment with isoniazid led to practically complete disappearance of all symptoms after a 40-day period of treatment with isoniazid. After treatment was terminated, on the 46th to the 53d day, all eyes remained free of treatment for a period of 56 to 66 days, when the first recurrences were noted. At the end of the experiment there were 20 survivors in these two groups. Thirteen of these, or approximately two-thirds, had recurrences during this period, while seven, or one-third, of the survivors remained free of all visible symptoms. This initial control with a high recurrence rate indicated a bacteriostatic, rather than a bacteriocidal, action against the Myco. tuberculosis.

C. Acquired Resistance to Isoniazid.—On July 28 the eyes of all Group I rabbits in both Experiment I and Experiment II had developed active tuberculous disease. At that time there were 10 survivors in Experiment I and 12 survivors in Experiment II. These Group I rabbits in each experiment were then divided into two subgroups I A and I B. Treatment was recommenced in the Group I B rabbits on July 28 and continued until Nov. 10. Group I A rabbits were left untreated, as controls.

The results in Experiment I are shown in Chart 5. There was no statistical difference between the behavior of the Group I A and that of Group I B rabbits. Both groups showed a steady decrease in the tuberculous disease. On Dec. 4, at the conclusion of the experiment, there were five survivors in Group I A. One of these showed low-grade activity; two showed burned-out and inactive tuberculosis with severely damaged eyes, and two were entirely inactive with only moderate residua. At the end of the experiment there were three survivors in subgroup I B

The eyes of these rabbits had been active when the second course of treatment was begun. In one rabbit the disease had become inactive after eight weeks' treatment; in one, after 9 weeks' treatment, and in the last, after 12 weeks' treatment. Since the eyes of the controls (subgroup I A) had similarly cleared, the observations do not indicate any therapeutic effect from the second course of treatment and suggest

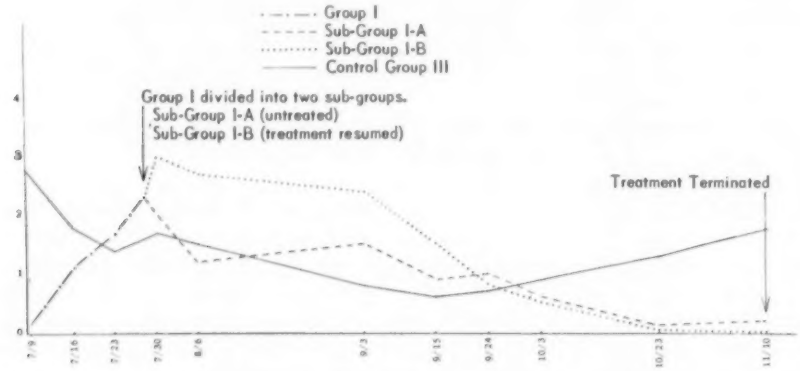

Fig. 5 (Experiment I).—Acquired bacillary resistance. Group I rabbits: ocular lesions developed three weeks after cessation of treatment, on June 18; treatment resumed in Subgroup I B on July 28.

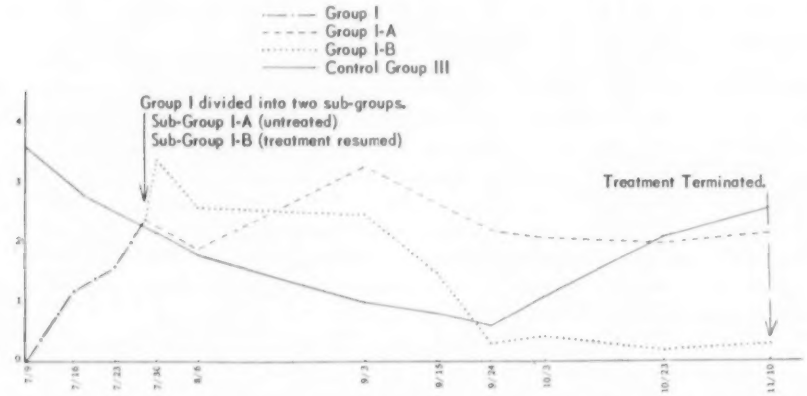

Fig. 6 (Experiment II).—Acquired bacillary resistance. Group I rabbits: ocular lesions developed three weeks after cessation of treatment, on June 18; treatment resumed in Subgroup I B July 28.

a partial acquired bacillary resistance. Both Subgroup A and Subgroup B were, however, definitely better than the untreated controls in Group III.

The results in Experiment II are shown in Chart 6. In this group of young pigmented rabbits, the second course of isoniazid in Group I B had a definite therapeutic action in three of the five treated rabbits, while two appeared resistant. In Group I A the disease continued unabated, and at the conclusion of the experiment was at approximately the same level as the disease in the totally untreated controls

of Group III. At the conclusion of the experiment, on Dec. 4, there were six survivors in Group I A, all of whom showed active tuberculosis and three showed advanced caseation and rupture. In Group I B there were five survivors. In three of these the second course of treatment had controlled the disease and the eyes appeared entirely quiet. In two rabbits the disease was uncontrolled; the eyes had developed caseous tuberculosis despite the treatments, and that subsided only after rupture of the globe. Thus, the second course of treatment had therefore been efficacious in three of the five survivors and had been without effect in two animals, the eyes developing caseous tuberculosis.

In summary, in these two experiments there was evidence of acquired bacillary resistance to isoniazid in five of eight eyes. Three rabbits responded fairly well to the second course of isoniazid, and it is probable that the existing organisms were still relatively sensitive to the drug.

COMMENT

When a proper dose of virulent human tubercle bacilli is injected into the anterior chamber of the eyes of normal rabbits, there is an incubation period of varying degree before actual tuberculous lesions appear in the eyes. The length of this incubation period varies from a few days to a maximum of about two weeks, according to the magnitude of the inoculum. In these experiments it was about 8 days in the adult albino rabbits and 12 days in the young pigmented rabbits. During this incubation period the organisms propagate on the eye until the infecting inoculum is of sufficient intensity to overcome any natural resistance possessed by the animal, at which time the bacilli invading the tissues produce lesions.

The positive findings in the portion of the experiments dealing with the inhibitory action of isoniazid were (*a*) that this drug, administered to the rabbits from the time of inoculation of the eyes completely inhibited the outbreak of visible evidences of ocular tuberculosis during the entire period of treatment and for three weeks thereafter, and (*b*) that three weeks after cessation of treatment, 100% of these treated rabbits developed the usual ocular tuberculosis seen in normal animals.

The conclusion is inescapable that the isoniazid had a complete bacteriostatic action on the injected bacilli and prevented their propagation during the period of treatment, and probably for some time thereafter. In addition to this bacteriostatic action, it is possible that a certain number of the injected bacilli were actually destroyed, because after cessation of treatment there was a latent or incubation period of three weeks before the development of lesions, while in the untreated controls the incubation periods were 8 and 12 days in the two experiments. This would indicate either (*a*) that the isoniazid or the natural resistance destroyed a portion of the injected organisms, or (*b*) that the inhibitory action of the isoniazid persisted for some days after the drug was withdrawn. There is no way of identifying either of these possibilities as the responsible factor for the long latent period from cessation of treatment to the outbreak of symptoms, although the experiment of Manthei and associates [18] indicates that isoniazid remains in the tissues in significant quantities for at least four days. One thing, however, can certainly be said. Under the conditions of this experiment, in which 100% of the treated animals later developed the lesions of ocular tuberculosis, any bacteriocidal effect exerted by the isoniazid must have been extremely small.

The marked bacteriostatic and weak or no bacteriocidal action of isoniazid is not so clearly shown in the experiments on the therapeutic action of the drug. In Experiment I, treatment with isoniazid was begun 10 days after inoculation, and in Experiment II, 20 days after inoculation. In Experiment I, a therapeutic response was noted after five days' treatment and in Experiment II, after 14 days' treatment. Whether this therapeutic effect was due solely to the bacteriostatic action of isoniazid, inhibiting the growth and propagation of the bacilli, while the natural or gradually developing acquired resistance controlled the early lesions, or to some bacteriocidal action of isoniazid is a question that cannot be definitely answered from these experiments. In view of the very doubtful evidence of any bacteriocidal action of isoniazid shown by the experiments on inhibition, it would seem probable that the inhibition of growth and propagation of the bacilli, plus natural or acquired resistance, were the factors responsible for the therapeutic effect.

This assumption is made more probable by a study of the incidence of recurrences in Groups I and II in the two experiments. In the inhibition part of those experiments (Group I) there was 100% incidence of tuberculous lesions after cessation of the drug. It should be noted that the rabbits in this group, although inoculated with bacilli, had suffered no ocular lesions prior to the later outbreak of the disease. Furthermore, the outbreak of lesions occurred two months after inoculation and three weeks after cessation of treatment. In the absence of early tuberculous lesions, there is no reason to assume that these animals would have developed any degree of acquired immunity. On the other hand, only 66% of the rabbits in Group II had recurrences. All of these animals had undergone an attack of active ocular tuberculosis, and recurrences came on from the 46th to the 66th day after termination of treatment and approximately 4 months after inoculation. In a previous paper,[25] the increased resistance to reinoculation of eyes which had undergone previous tuberculous disease was noted. Also, by four months after inoculation, all of these animals in Group II should have developed definite acquired resistance. It is therefore probable that the decreased incidence of the disease after cessation of treatment in Group II rabbits, as compared with Group I rabbits (66% against 100%), was due to local and systemic acquired resistance. With this evidence of a developing acquired immunity, it is probable that such immunity was concerned in the therapeutic result, once bacteriostasis had been accomplished by isoniazid.

The question of acquired bacterial resistance to isoniazid after prolonged treatment is of interest, but, unfortunately, the number of rabbits in which this question could be explored was so small that the result is of questionable statistical significance. In Experiment I, Group I B, three animals with recurrent ocular tuberculosis were retreated. Whereas on the first course of treatment a therapeutic effect was noted within five days, in these three rabbits the disease burned out in 8, 9, and 12 weeks, at the same time as in the untreated controls. The disease in the treated animals was, however, somewhat less intense than in the controls. In Experiment II, five rabbits with recurrent ocular tuberculosis were given a second course of isoniazid, and in three there was a delayed, but quite appreciable, therapeutic effect. In two the drug was then without effect, the disease proceeding to rupture of the globe. Thus, in five of the eight retreated animals the second course of treatment appeared without effect, while in three rabbits the bacilli appeared still sensitive to the drug, but to a less extent than on the first course of treatment.

At the time the animals were killed, the eyes of 22 rabbits in various groups were cultured for the presence of tubercle bacilli, with the idea of testing any recovered organisms for susceptibility to isoniazid or for the development of bacterial resistance to the agent. [The distribution and results of these cultures, together with the clinical and histological findings in the eyes, are shown in Table I.]

Thus, 19 of the 22 eyes cultured showed viable tubercle bacilli, while 3 cultures were negative. One of the negative cultures was from a ruptured eye which both clinically and histologically showed advanced caseous tuberculosis. The negative culture for tubercle bacilli in this eye must be considered a laboratory error or the result of the massive secondary infection. A second eye, negative on culture, was also negative clinically but on histological examination showed one small active tuberculous focus. The negative culture in this eye was probably due to culture of noninfected tissue. In the third eye with a negative culture there was no clinical or histological evidence of active tuberculosis, and it is a fair conclusion that this eye, in a Group II B rabbit subjected to two courses of isoniazid, was actually sterile. Thus, in only one of the 22 eyes cultured was there any conclusive evidence of a bacteriocidal action of isoniazid.

Since a number of these eyes had ruptured, with consequent secondary infection, the majority of the cultures showed a mixed flora, and considerable difficulty was encountered in getting the Myco. tuberculosis out in pure culture. This was finally accomplished in all 19 instances. In vitro studies for acquired bacillary resistance to isoniazid by the organisms cultured from the various groups were made, but the results were inconclusive.

The moral of these experiments appears self-evident. In isoniazid we have an agent with a prompt bacteriostatic action against the Myco. tuberculosis, but with a weak or no bacteriocidal action. Therefore, theoretically it should be combined with agents of proved bacteriocidal action, such as streptomycin, with PAS, or thiazolsulfone as an adjuvant, employing isoniazid to inihibit the growth and propagation of the bacilli and the streptomycin plus the adjuvant to destroy them. This is the program we are now employing in the treatment of clinical ocular tuberculosis. There appears to be no contraindication to such combined treatment; in fact, a preparation of streptomycin combined with isoniazid will soon be on the market for clinical use. While it is difficult to compare different forms of effective treatment in clinical cases, nevertheless it is our distinct impression that treatment with isoniazid together with streptomycin and the adjuvant has given a prompter, and possibly a better, therapeutic response than has streptomycin and the adjuvant alone. Experiments in animals to clear this point are now in progress.

SUMMARY

1. Isoniazid in normal, nonimmune rabbits has a marked inhibitory effect on the development of ocular tuberculosis, completely inhibiting the outbreak of the disease while the animals are under treatment and for three weeks thereafter.

It appears this inhibitory action is due to bacteriostasis, rather than to a bacteriocidal action.

2. Isoniazid administered to normal, nonimmune rabbits after the outbreak of manifest tuberculous ocular lesions has a marked therapeutic effect.

It appears this therapeutic effect is due to a bacteriostasis induced by the drug and the natural or acquired resistance of the experimental animal.

3. There is a definite tendency for the treated animals to develop a bacillary resistance to the drug.

These experiments suggest that in the treatment of clinical ocular tuberculosis isoniazid should be combined with streptomycin and some adjuvant.

REFERENCES

1. Fox, H. H.: The Chemical Approach to the Control of Tuberculosis, Science **116**:129, 1952.

2. Woods, A. C.; Wood, R. M., and Naquin, H. A.: Studies in Experimental Ocular Tuberculosis: XIII. Effect of Streptomycin and Promizole® in Experimental Ocular Tuberculosis in the Normal Rabbit, Arch. Ophth. **43**:834, 1950.

3. Woods, A. C.; Wood, R. M., and Naquine, H. A.: Studies in Experimental Ocular Tuberculosis: XV. Effect of Paraaminosalicylic Acid and of Streptomycin Plus Paraaminosalicylic Acid in Normal Rabbits, A. M. A. Arch. Ophth. **45**:546, 1951.

4. Bietti, G. B.: Use of Paraaminosalicylic Acid Alone or in Association with Streptomycin in Ocular Tuberculosis: Experimental and Clinical Investigations, Arch. Ophth. **43**:431, 1950.

5. Woods, A. C.: Therapeutic Action of Streptomycin and Promizole® in Clinical Ocular Tuberculosis: A Preliminary Report, Arch. Ophth. **42**:521, 1949.

6. Rist, N.; Bloch, F., and Hamon, V.: Action inhibitrice du sulfamide et d'une sulfone sur la multiplication in vitro et in vivo du bacille tuberculeux aviaire, Ann. Inst. Pasteur, **64**:203, 1940.

7. Feldman, W. H.; Hinshaw, H. C., and Mann, F. C.: Promizole in Tuberculosis: Effect on Previously Established Tuberculosis of Guinea Pigs of 4,2'-Diaminophenyl-5'-Thiazolylsulfone (Promizole), Am. Rev. Tuber. **50**:418, 1944.

8. Lehmann, J.: Determination of Pathogenicity of Tubercle Bacilli by Their Intermediate Metabolism, Lancet **1**:14, 1946.

9. Domagk, G.: Über eine neue gegen Tuberkebazillen in vitro wirksame Verbindungsklasse, Naturwissenschaften **33**:315, 1946.

10. A New Drug in the Treatment of Tuberculosis, Editorial, J. A. M. A. **142**:342, 1950.

11. Chorine, V.: Action de l'amide nicotinique sur les bacilles du genre Mycobacterium, Compt. rend. acad. sc. **220**:150, 1945.

12. Meyer, H., and Malley, J.: Monatsschr. Chim. **33**:393, 1912.

13. Grunberg, E., and Schnitzer, R. S.: Studies on the Activity of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis of Mice, Quart. Bull. Sea View Hosp. **13**:3, 1952.

14. Steenken, W., Jr., and Wolinsky, E.: Antituberculous Properties of Hydrazines of Isonicotinic Acid (Rimifon, Marsilid), Am. Rev. Tuberc. **65**:365, 1952.

15. Bernstein, J.; Lott, W. A.; Steinberg, B. A., and Yale, H. L.: Chemotherapy of Experimental Tuberculosis: V. Isonicotinic Acid Hyrazide (Nydrazid) and Related Compounds, Am. Rev. Tuberc. **65**:357, 1952.

16. Rubin, B.; Hassert, G. L., Jr.; Thomas, B. G. H., and Burke, J. C.: Pharmacology of Isonicotinic Acid Hydrazide (Nydrazid), Am. Rev. Tuberc. **65**:392, 1952.

17. Benson, W. M.; Stefko, P. L., and Roe, M. D.: Pharmacologic and Toxicologic Observations on Hydrazine Derivatives of Isonicotinic Acid (Rimifon, Marsilid), Am. Rev. Tuberc. **65**:376, 1952.

18. Manthei, R. W.; Roth, L. J.; Barclay, W. R., and Ebert, R. H.: C^{14} Isoniazid Concentration in Normal and Tuberculous Tissues, Fed. Proc. **12** (Pt. 1):348, 1953.

19. Selikoff, L.; Ornstein, G. G., and Robitzek, E. H.: Toxicity of Hydrazine Derivatives of Isonicotinic Acid in the Chemotherapy of Human Tuberculosis, Quart. Bull. Sea View Hosp. **13**:17, 1952.

20. Bosworth, D. M.; Wright, H. A., and Fielding, J. W.: Marsilid in the Treatment of Tuberculous Orthopedic Lesions: A Preliminary Report, Quart. Bull. Sea View Hosp. **13**:52, 1952.

21. Elmendorf, duM. F., Jr.; Cawthon, W. U.; Muschenheim, C., and McDermott, W.: The Absorption, Distribution, Excretion and Short-Term Toxicity of Isonicotinic Acid Hydrazide (Nydrazid) in Man, Am. Rev. Tuberc. **65**:429, 1952.

22. Robitzek, E. H., and Selikoff, I. J.: Hydrazide Derivative of Isonicotinic Acid (Rimifon, Marsilid) in the Treatment of Active Progressive Caseous-Pneumonic Tuberculosis: A Preliminary Report, Am. Rev. Tuberc. **65**:402, 1952.

23. The Treatment of Pulmonary Tuberculosis with Isoniazid, An Interim Report to the Medical Research Council by Their Tuberculosis Chemotherapy Trials Committee, Brit. M. J. **2**:735, 1952.

24. Fust, B.; Brückner, R., and Studer, A.: Therapeutische Beeinflussung der experimentellen Augentuberkulose der Kaninchsen durch Rimifon (Isoniazid), Ophthalmologica **125**:1, 1953.

25. Woods, A. C., and Burky, E. L.: Experimental Studies of Ocular Tuberculosis: VIII. A Study of the Increased Resistance to Reinoculation After Recovery from Ocular Tuberculosis Shown by the Immune-Allergic Rabbit, Arch. Ophth. **31**:413, 1944.

Annual Reviews

CORNEA AND SCLERA

Review of the Literature

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ANATOMY AND PHYSIOLOGY

IN DOING routine laboratory examinations on eyes with edema of the cornea and bullous keratitis, Irvine and Irvine [1] have noted microscopic changes in the endothelium, even though there was no striking evidence of edema in the fixed specimen. The nuclei were flattened, attenuated, and reduced in number. In order to determine the normal concentration of epithelial cells on the posterior surface of the cornea, flat preparations were made and stained with hematoxylin, and the nuclei were counted within a grid field in a manner similar to that used in counting blood cells. There was no significant effect of either age or difference in duration of fixation, but there was great difference among individual normal eyes irrespective of their age. Five abnormal eyes were studied. One presented an abnormally high concentration of cells, possibly attributable to extreme dehydration preceding death. The remaining four had abnormally low concentrations of endothelial cells. These low counts were thought to represent changes secondary to intraocular processes. Such low cell concentrations are thought to interfere with the normal endothelial function of preventing corneal hydration.

Teng and Katzin [2] give a preliminary report on their continuing histological studies of the cornea. Using Friedenwald's periodic-acid-fuchsin stain, they have observed that the corneal epithelium has a very definite basement membrane, which is distinguishable from Bowman's membrane. It is found between the epithelial layer and Bowman's membrane. It varies in thickness from the width of an epithelial cell to one-third the thickness of Bowman's membrane. It stains strikingly purple with the periodic-acid-fuchsin stain. A review of the older literature reveals several reports describing what is believed to be the same structure.

Aurell and Holmgren [3] have made what appears to be an important study of corneal collagen with special reference to its metachromasia, its refractive index, and its capability of swelling. The mucoid contents of the cornea and sclera were investigated with the aid of special staining methods. The corneal mucoid was dissolved in running water for 48 hours. If the cornea and sclera prepared in this manner were placed in a solution of mucoid, only the corneal collagen absorbed the metachromatic substance again. Ordinary tendon tissue and scleral tissue, as well as connective tissues, do not absorb the metachromatic substance except that connective tissue may in some cases absorb very small amounts. Therefore corneal collagen differs from the majority of other collagens of the body in its capacity to absorb metachromatic substance. Therefore the pronounced capacity of swelling the cornea displays when placed in water is a characteristic which chiefly resides in the collagen of the stroma. It is demonstrable only to a very slight degree in

the so-called intermediary substance. The authors conclude that the cornea remains transparent within much wider limits of refractive index of the permeating fluid than is the case with other collagenous organs.

Smelser,* too, has made investigations in regard to this subject. Histological studies of fish and guinea pig corneas show that the quantity of corneal mucoid is much less in the fish than in the mammalian cornea. The swelling power of excised fish cornea in saline solution is definitely less than that of mammalian cornea. This difference may be due to the lower mucoid content indicated by the histological studies. Furthermore, in the study of the corneas of fish it was found that, although the fish and mammalian corneas were qualitatively similar, they were quantitatively very different. In each medium studied the swelling of the aquatic cornea was much less than that of the air type. This difference was independent of whether the cornea was exposed to salt solution isotonic to that species or to distilled water, or whether the corneas had been deprived of the epithelium or were intact. An explanation was possibly found in the fact that there was distinctly less mucoid in the corneal stroma of the aquatic eye than in that of the mammalian eye. This was indicated by the degree of metachromasia to toluidine blue and the periodic-acid-Schiff reaction.

Smelser and Ozanics [4] also report their careful investigation of corneal changes after the wearing of contact glasses. Conventional type lenses were made for guinea pigs, who wore them from 30 minutes to 8½ hours, always with a 1.5% solution of $NaHCO_3$. A corneal haze, similar to that produced in man, occurred in about the same time as it does in man when the same solutions were employed. Associated with the haze was an increase in the corneal thickness, which has also been shown to occur clinically. This increased thickness was found to be due to thickening of the stroma but not of the epithelium. The stromal swelling was seen histologically to be due to separation of the lamellae and connective tissue fibers by spaces which in life were presumably filled with water. The authors found that the glycogen stores of the corneal epithelium were rapidly exhausted when contact glasses were worn. This occurred prior to pronounced corneal edema, swelling, and haze. It was thought that when the glycogen reserve was exhausted, water entered the cornea more rapidly than it could be removed and the cornea again swelled. These authors have also developed apparatus for measuring corneal turbidity and thickness. The thickness of the cornea increased during the period of wearing contact glasses, but the rate of increase was not the same for corneal thickness and turbidity. These observations confirmed those made on man and, therefore, add greater significance to the study of the structural and chemical changes in the cornea of the guinea pig which are caused by wearing contact glasses.

Bock and Maumenee [5] have devised a most interesting surgical experiment to test the theory of corneal deturgescence through osmosis (Cogan and Kinsey), in which the epithelium and endothelium act as semipermeable membranes. The two semipermeable membranes were eliminated by introducing one transparent, inert, and water-impermeable film as closely as possible beneath the epithelium, and another over the endothelium. This was cleverly done through a surgical incision (under a conjunctival flap 2 mm. above the upper limbus). Thin polyethylene sheets were used. Four of nine rabbits so prepared were suitable for observation. Immediately after the operation all three layers of the corneal stroma appeared equal.

* Smelser, G. K.: Personal communication to the author.

After three to four hours the surface layer became gray and edematous. The middle and posterior layers appeared normal. After 48 hours the picture had not changed. When only one sheet of polyethylene was introduced, in the midstroma, dividing the cornea into two layers, the same picture resulted, namely, edema of the anterior layer only. Three corneas with two polyethylene sheets were examined histologically two days after implantation. The epithelium was found absent over the central area. Centrally, cells had disappeared in the superficial stromal layer. The middle layer, between the two films, showed similar changes, but to a slighter degree. In the layer behind the deeper film the stromal cells were normal, as were Descemet's membrane and the endothelium.

The authors attempted to control their experiments by producing similar surgical trauma, that is, removing the films after operation. They also introduced perforated films. No edema of the overlying layer could be observed in these cases.

The authors conclude that osmotic forces acting through epithelium and endothelium as semipermeable membranes are not solely responsible for the state of deturgescence of the cornea, since a layer of cornea isolated mechanically from these membranes remains free of edema and clear for at least 48 hours. Corneal stroma when separated from the endothelium and aqueous rapidly degenerates even if connection with the limbus is present. The authors suggest that diffusion across the cornea to or from the aqueous of substances vital to this tissue is essential to the survival of stromal cells. The existence of the central corneal epithelium also appears to be dependent on this diffused substance or on the survival of the underlying corneal stromal cells.

Potts [6] has studied the problem of corneal transparency and the tonicity of tears by carefully devised experiments in rabbits. He has demonstrated the rate of transfer of inorganic ions across the corneal epithelium and endothelium in both directions. The results of these experiments indicate that, in agreement with previous work, the corneal epithelium has low permeability to inorganic salt in both directions but that, in contrast to this, the corneal endothelium is relatively freely permeable to salts, certainly from cornea to aqueous and possibly from aqueous to cornea. The author concludes that the presently accepted theories of corneal dehydration mechanisms require revision. He also concludes that the osmotic concentration which does least damage to the corneal epithelium is equivalent to 1.35% sodium chloride. This, by inference, is the tonicity of tears.

In his discussion of this paper, Cogan † points out the confusion that these experiments brought out, since two seemingly similar experiments indicate opposite conclusions. He points out that Potts's experiments indicate that the endothelium is relatively freely permeable to sodium and to other ions and that there is no real evidence that the endothelium was damaged in his procedure. Yet it appears that the endothelium is permeable to these ions in both directions in the living animal. The experiments of Cogan and Kinsey on enucleated eyes indicated that the epithelium is impermeable to electrolytes, as Potts has shown.

Potts's observations and those of Cogan and Kinsey seem to be contradictory. The latter were made on the enucleated eye. Potts's were made on the living eye. One would expect that such a membrane would be permeable during life, that in death it would lose this property and become freely permeable; but the opposite

† Cogan, D. G., in discussion on Potts.[6]

seems to be the case in Potts's experiment. Potts finds that the membrane in the living animal is readily permeable, while Cogan and Kinsey found that in the enucleated eye it was impermeable. The experiments seem contradictory and require further study.

ULCERATIVE AND NONULCERATIVE KERATITIS

Ulcus Serpens.—Fedukowicz and Horwich [7] give an interesting report on their investigation of six patients with hypopyon keratitis due to a Gram-negative diplobacillus seen at Bellevue Hospital in New York. The literature is reviewed, with special reference to the early papers by Morax (1896), Axengeld (1897), and Petit (1898).

In this study, organisms were recovered from unquestionable cases of Morax-Axenfeld conjunctivitis and were compared with organisms from their cases of hypopyon keratitis to see whether there was any bacteriologic basis for the belief that the conjunctivitis must be due to the Morax-Axenfeld bacillus and central hypopyon ulcer to the diplobacillus of Petit. The organisms were compared in direct smear, in culture, and in animal pathogenicity. In none of these studies were significant differences found between the organism recovered from the cases of conjunctivitis and those recovered from the cases of central hypopyon ulcer.

The authors believe that the clinical differences depend on local differences between the peripheral and the central portion of the cornea and the general constitution of the patient. Their six patients were all chronic alcoholics.

In most cases of central corneal ulcer with hypopyon seen at Bellevue Hospital, the infecting organism appeared to be a Gram-negative bacillus, especially the Morax-Axenfeld bacillus. This is in contrast to the high incidence of pneumococcic ulcers reported elsewhere.

The most dramatic clearing of the inflammatory reaction was noted with the use of chloramphenicol. Other antibiotics and chemotherapy were less effective. The authors strongly recommend supportive treatment, rest, a nutritious diet, and vitamins. The value of zinc sulfate should not be overlooked, perhaps in stronger concentrations than are ordinarily used.

The incidence and present treatment of ulcus serpens are reported on by Bambert,[8] from Basel, who finds that the incidence has not decreased during the past 25 years. The results of treatment indicate that penicillin is far more effective than either Optochin and silver or the sulfonamides. The incidence with Pneumococcus as the cause decreased from 65 to 20%; that with Staphylococcus during the same period from 20 to 45%.

Belmonte-Gonzalez [9] reports that an Amsler puncture was made in 30 cases of corneal ulcer. Examination showed that in serpiginous nonperforating ulcer, suppurative micro-organisms were present in the anterior chamber, but, unfortunately, it was not possible to differentiate the cytologic or bacteriologic data of favorable and unfavorable cases, so that this procedure could not be utilized for a prognosis. The use of chlortetracycline (Aureomycin) ointment seemed to give the best results.

Interstitial Keratitis.—Perhaps the most interesting report on interstitial keratitis that has appeared during the past year, exclusive of reports of its treatment with cortisone, comes from Oksala.‡ In a short historical review the writer men-

‡ References 10 and 11.

tions the opinion at present so widely held, that interstitial keratitis and persisting chorioretinitis are two distinct conditions. Up to the present there has been the widest support of Igersheimer's views among research workers. According to Igersheimer, primary specific interstitial keratitis without choroiditis is the rule. He finds that there is a connection between the uvea and the cornea only through the circumstance that spirochetes enter the two tissues at the same time but that the uvea, nevertheless, becomes diseased much sooner. Heretofore, study of the fundus during the course of the keratitis has in most cases been unfeasible. Through a cornea made transparent by means of cortisone the author was able to follow the changes in the fundus during the active stage in a case of interstitial keratitis associated with congenital syphilis. During the treatment the formation of a large chorioretinal patch in the fundus was revealed. The finding is thought to point to a closer relation than has heretofore been supposed to exist between interstitial keratitis and chorioretinitis. In the case described, cortisone treatment seems to have had a rapid but notable transitory effect, since the disease became reactivated four times shortly after cortisone had been discontinued.

Herpes Corneae.—Thygeson [12] feels more strongly than ever that herpes corneae is the most important specific keratitis in the United States. Prior to World War II, he had observed only one case of bilateral dendritic keratitis in 14 years, but during the war he saw several and recently he observed three in a single week. It is his impression that the disease has increased steadily in severity and in frequency. Furthermore, there seems to be a higher incidence of associated lesions, such as disciform keratitis and uveitis. He also observed an extraordinary increase in the number of cases of primary ocular herpes in which the severe conjunctivitis and preauricular adenopathy resemble the changes seen in epidemic keratoconjunctivitis.

Prior to the advent of cortisone, corneal perforation was an unheard-of complication in herpes corneae and hypopyon was exceedingly rare. He has now seen two cortisone-treated patients with hypopyon and has heard of three with corneal perforation.

Thygeson summarizes our experience for the past 25 years [12]:

> There has accumulated a great deal of knowledge on the epidemiology, the immunology, and the biologic and morphologic properties of herpes simplex virus, while little or no progress has been made in the field of therapy. Early hope that aureomycin, or other broad-spectrum antibiotics, would be effective has faded, and attempts at hyperimmunization for the prevention of recurrences have in general been unsuccessful. The only hope for therapy still rests in the local destruction of the virus in the affected tissues.

Thygeson feels that the prospects of therapeutic advance in herpes lies in the hope of finding a way to interrupt by chemotherapy some essential process. This has been applied with outstanding success to bacteria, which are free-living; to the rickettsiae, which are intracellular, and to the atypical viruses of the psittacosis-trachoma-lymphogranuloma venereum group, which are also intracellular.

The author recommends that, while awaiting therapeutic advances, effort should be made to interrupt the various trigger mechanisms which are in many cases concerned with recurrences. The use of antipyretics and antihistaminics is certainly worthy of trial when fever is a precipitating cause or when such other activating mechanisms as sunburn, menstruation, emotional crisis, and allergy are known to be concerned.

The evidence is now accumulating from both clinics and laboratories that cortisone has a masking effect only in this disease. In spite of the fact that herpetic patients often feel more comfortable while taking cortisone and that a few isolated reports on favorable effects have appeared, only harm can be expected from its widespread use. There are now on record a number of instances in which dendritic keratitis has developed in patients undergoing systemic or topical cortisone therapy, and it should be emphasized that in three of the five very severe cases referred to in this article the disease had been treated with cortisone.

Braley,[18] in the Sanford R. Gifford lecture on experimental herpes simplex, makes an excellent summary on the history and development of our knowledge of this disease up to the present time and brings us up to date on his extensive researches and clinical experience with this disease.

The author agrees with other workers that the first herpes simplex infection takes place in infancy or childhood as an aphthous stomatitis and that the virus then remains in the mouth for life. He agrees with the researches of Burnet, who has shown that persons susceptible to herpes have circulating serum antibodies to the virus. It is not clear whether or not he agrees with Burnet that in herpes simplex there is an "all-or-nothing response"; either the antibody titer is high or there is none. The author claims that certain classes of people show larger numbers with serum antibodies than other classes of people. Herpes simplex antibodies are found in 90% of the lower classes, while in the higher classes, such as university students, only 30 to 35% have antibodies. Four types of herpes infection are described.

1. An acute primary herpes simplex blepharoconjunctivitis. In this type the cornea usually shows a distinct dendritic figure, and it is not unusual that the corneal epithelium is denuded entirely. Regional lymph nodes are involved. There are no serum antibodies during the acute phase of the disease but they develop slowly after the disease has run its course and becomes chronic, and at the end of 30 days definite titers can be measured by mouse neutralization tests. It takes about 60 days for the highest titers to be demonstrated.

2. Self-limited, recurrent dendritic ulcer of the cornea without conjunctivitis. Braley believes that a person who develops this type of the disease must have the virus in his conjunctival sac at all times. He has found these lesions to run a course of 5 to 14 days. The virus then returns to its latent state in the cells, awaiting the proper stimulus to produce another lesion. These stimuli may be any of the following: radiant energy on the eye; fever, such as that in malaria; cortisone applied to the cornea or liberated from within, and emotional disturbances. In the last the mechanism may be by overstimulation of the adrenal and subsequent release of cortisone.

3. Disciform keratitis. This is thought to be a type of collagen reaction similar to the reaction that is produced in the cornea with scrofula, acne, and other disease. Braley believes that this represents a hypersensitivity to herpes and that the virus acts as an antigen and combines with the local and circulating antibodies to produce a hypersensitivity reaction. The evidence for this hyperimmunity is borne out by some experimental evidence. Braley, contrary to the opinion of many others, believes that clinial experience has shown that cortisone is effective in treatment of disciform keratitis.

4. Keratitis metaherpetica. This condition is described carefully, and it is interesting that the author has cultured virus from two of three cases, though he admits it is very difficult. The development of keratitis metaherpetica is explained by an unusual growth of the epithelial cells in their attempt at healing. It is claimed that it is the second and third layer of cells in the epithelium that fill in the defect produced by the ulcer. These cells also phagocytose any free virus that may be present and tend to fix the virus in the nuclei. In this disease, then, a certain amount of fluid collects between these large cells and Bowman's membrane. Bullae are supposed to be formed. The author also feels that keratitis metaherpetica may be a hyperimmune state, much like the disciform type of keratitis. He advocates treatment by introducing the interference phenomenon. This is accomplished by repeated vaccinations with vaccinia virus. The evidence of success in this treatment is not very abundant. Braley carefully discusses the strain differences of herpes. One strain always produces encephalitis in rabbits after corneal inoculation, with death of the rabbit in seven days. Another strain rarely produces encephalitis. Immunologically, however, there does not appear to be any difference in the various strains.

The usefulness of chlortetracycline (Aureomycin) is discussed in detail. The encouraging early reports of the usefulness of this antibiotic have not stood the test of time. Braley believes that crude chlortetracycline is more effective, and he has searched for a substance that was removed from the original product. The first substance studied was folic acid. It is said that in tissue cultures the virus grows until all cell nuclei are filled with virus. When the cell nuclei are filled with virus, the cells and virus lie dormant. If the cell nuclei have combined with enough folic acid, it is not possible to infect the cells with herpes virus. However, folic acid and folic-acid antagonists have proved to have no value in the treatment of the clinical disease.

Rossetti and Borio [14] report an analysis of 104 cases of herpetic keratitis seen in 16 years; and since their findings vary considerably from the generally accepted ideas of this disease, they are worth reporting. These cases comprise 1.05% of patients seen in their clinic. As etiologic factors responsible for ocular herpes the authors list the following: trauma, 21%; malaria, 10%; focal sepsis, 21%; neuroendocrine disturbances, 18%; tuberculosis, syphilis, and unknown causes, 14%. Most of their patients were adults, and 70% were men. The last finding, I believe, corresponds to that generally accepted, but the authors report an increasing incidence with advancing age, a finding which is contrary to the idea generally accepted. They also believe that an allergic reaction may be of etiologic importance.

Epidemic Keratoconjunctivitis.—The literature on epidemic keratoconjunctivitis has been rather sparse during the past year. Arakawa and his co-workers [15] report that they have isolated eight strains of virus from patients with this disease. Two strains were recovered from the conjunctiva, six from the serum, of patients. The virus could be cultivated in developing chicken embryo and also maintained in mouse brain. Neutralizing antibodies were found in convalescent serum, but the titer was low in patients with actual punctate keratitis. Conjunctivitis was produced in one monkey by massive subcutaneous and intravenous inoculation of the virus.

A real epidemic of keratoconjunctivitis has recently occurred in Vienna and is reported by Pillat.[16] He observed 217 cases in 40 days. In 55% the cornea was involved. He was able to transmit the disease to rabbits. The author does not believe

that the virus penetrates to the interior of the eye, and he is of the opinion that antibiotics and cortisone do not influence the course of the disease.

Superficial Punctate Keratitis.—The most noteworthy article on superficial punctate keratitis during the past year is that by Braley and Alexander.[17] The authors describe the disease as similar to that recently described by Thygeson (1950). It is bilateral and shows epithelial and subepithelial opacities. The opacities are centrally located on the cornea and are more numerous on the upper half. Nine patients with the disease have been followed for a period of four to eight years. The opacities are irregular in shape, roughly oval vertically, and consist of tiny white or gray dots. This explains their stippled appearance. Their centers stain irregularly. There is no conjunctivitis, and usually cultures are negative. Uniform hyperemia of the blood vessels extends from the superior rectus to the upper limbus, but usually the eye is elsewhere white.

Normal remissions occur, and lesions come and go rapidly. During an attack 12 or more opacities may be seen; during remissions only 1 to 2. Sensation is normal or slightly decreased. The disease occurs in nervous, impatient patients who appear psychologically disturbed, and the authors are sure that cases are often overlooked. They describe the life cycle of the lesion. With the rapid growth of the lesion the necrotic center falls out, causing a tiny filament to form. Some lesions may require 12 hours to appear and disappear.

From one patient authors were able to grow and transmit a virus in tissue culture, as well as in mouse brain, and from mouse brain again to two of four rabbit corneas, with an incubation period of eight days.

Blood from eight patients was studied. Many showed only a suggestion of neutralizing antibodies. Experiments with herpes immunizing serum showed no cross immunization. In a control group of 56 patients with various ocular disease, 17 showed some neutralizing antibodies. Most of these 17 had nonspecific uveitis.

Skin tests were unpredictable. A positive reaction was usually present during an attack of the disease, and frequently the reaction was only mildly positive during a remission. All 17 patients who had some circulating antibodies showed a slightly positive reaction to skin tests.

The virus readily passes filters. Its exact size has not been determined, but it is thought to be very small, possibly in the neighborhood of 56 to 60 μ. No inclusion bodies have been found.

Seven of the nine patients were treated with intradermal and subcutaneous inoculations of the killed virus. There was wide variation in the effect. The first patient responded quickly. After five injections he showed a high serum antibody response and has had no further attack in five years. Five patients received no beneficial effect and after each inoculation showed a flare-up in the eyes.

Other treatments have been of little or no value. None of the antibiotic or chemotherapeutic agents have proved to be of any use. Likewise, curettage and cautery with I_2 gave no benefit. One patient showed improvement with cortisone drops; two, a pronounced increase in corneal opacities.

CORNEAL DISTURBANCES ASSOCIATED WITH METABOLIC OR SYSTEMIC DISEASE

Infantile Cystinosis.—Brœndstrup[18] describes two cases of the rare metabolic disease called infantile cystinosis. The disease was probably first described by Kaufmann (1902). Since 1924, the pathologist Lignac's name has been attached

to the disease. As late as 1949, Freudenberg could collect no more than 16 cases. An excellent account is given of this peculiar clinical picture, comprising retardation of growth, anorexia, polydypsia, polyuria, and albuminuria, as well as rickets. There is invariably an intravital accumulation of the sulfur-containing amino acid cystine in the cornea and conjunctiva. The occurrence of these crystals in the eyes affords the possibility of quick and easy verification of the diagnosis. Conjunctival biopsy is advocated.

Osteogenesis Imperfecta Congenita and Blue Sclerotics.—A. D. Ruedemann Jr.[19] has given an excellent clinicopathological study of this condition and carefully summarized the literature back to Ekmann's first description of the disease (1788). The author describes three cases of osteogenesis imperfecta diagnosed either clinically or pathologically. Two eyes were obtained at autopsy, and a third was enucleated for clinical reasons.

The blue appearance of the eyeball is due to scleral transparency. This may be due to several factors: (*a*) The fibrous coats are thinner; (*b*) the deficiency of collagen bundles and fewer fibers in a looser framework may reduce scattering of light, and (*c*) the increased density of staining with the periodic-acid-fuchsin technique suggests the possibility of a relative increase in the mucoid component of the tissue. The author points out that the term blue sclerotics is a misnomer—clear sclerotics is more indicative of the true histological character of this tissue. No indication was found for a possible relation of this disease to endocrine imbalance. Neither were hereditary factors brought out.

The abnormalities in the fibrous coats of the eye would appear to be similar to the changes in the bone and skin, namely, deficiency in collagen formation.

Polyarteritis Nodosa of the Eye.—Goar and Smith[20] add two cases which show eye involvement to the relatively few cases recorded. The histology of both cases is carefully described. The disease is described as a focal degenerative-inflammatory disease affecting the small and medium-sized arteries and is characterized by a peculiar type of hyalin-like necrosis known as fibrinoid degeneration. Around these areas quickly appear cells indicative of acute inflammation. The nodules from which the name is derived appear in only about 20% of cases and are caused by aneurysmal dilatation, exudation, and excessive fibrosis. In the eyes the characteristic changes are oftenest found in the choroid, but the retinal, ciliary, muscular, and episcleral arterial branches may be affected.

Gout.—McWilliams[21] gives an excellent, brief historical review of gouty disease of the eye. The characteristic clinical picture of ocular gout is described, which includes conjunctivitis, scleritis, episcleritis, iridocyclitis, tenonitis, and, rarely, keratitis. The case report of a man with gout is given. He had occasional attacks of arthritis for five or six years. The serum uric acid was reported as 11.4 mg. per 100 cc. When he was seen in the department of ophthalmology, University of Michigan, hard, white, chalky masses, 1-2 mm. in diameter, were noted in the position normally occupied by the pinguecula. A biopsy of one of these lesions in the fresh specimen revealed the presence of innumerable needle-like crystals characteristic of uric acid. This is thought to be the first case of conjunctival tophi reported.

Atopic Keratoconjunctivitis.—Hogan[22] describes five cases of atopic eczema with keratoconjunctivitis. The condition appears to be a specific entity, and the

diagnosis is based on the following findings: (*a*) a hereditary history of allergies; (*b*) associated allergies; (*c*) a typical persistent dermatitis with exacerbations and remissions; (*d*) keratoconjunctivitis, associated with activity of the skin condition and characterized by thickening and hyperemia of the conjunctiva and opacification and vascularization of the cornea, and (*e*), usually, an eosinophilia of the blood and the conjunctival secretion. A prompt response to treatment with cortisone hourly and topically occurred in all the author's cases.

Porphyria.—Barnes and Boshoff [23] describe the ocular lesions associated with porphyria which were present in 31 of 84 patients. Forty-two showed lesions of the fundus. Two could not be examined ophthalmoscopically. Particular attention is given to the fundus lesions.

The cornea may present a keratomalacic type of lesion. Lesions resembling groups of phlyctenules may precede actual corneal ulceration. Apparently, 22 patients in this series had disease of the cornea or sclera or both.

Ocular Pemphigus.—Soudakoff and Whalman [24] report the case history and the microscopic examination of an eye with pemphigus. Only five such corneas have heretofore been examined pathologically. The disease occurred in a 77-year-old white woman whose eye was removed for progressive corneal ulceration. The disease is described as a primary degeneration of the conjunctival mucosa and submucosa. The altered bulbar conjunctiva has a tendency to grow over the cornea, spreading between the epithelium and Bowman's membrane. The authors believe the edema of the epithelium, with separation from the stroma, forms vesicles and bullae and is due to diminished osmotic tension in the corneal epithelium caused by lack of tears. The vascular membrane developing beneath the corneal epithelium may erode Bowman's membrane.

Episcleritis and Erythema Nodosum.—Kratka [25] reports his studies on a 21-year-old white woman with erythema nodosum and describes it as part of the collagen syndrome. He agrees with the suggestions of Stillerman, Swan, and Klemperer that episcleritis can no longer be considered a local entity. The sclera must be considered as part of the other vital and interrelated tissues of the eye. He cites as evidence the dramatic response of these tissues to corticotropin and cortisone and feels that the disease represents an allergic (or hypersensitivity) type of response.

Scleromalacia.—Boehringer [26] describes the case history of a man with severe sepsis who died after 10 months. Two months after illness began scleromalacia developed in both eyes. Necrosis and sequestration of scleral lamellae followed. The author regards the condition as one to be distinguished from the nodular necroscleritis and scleromalacia with porphyrinuria.

François [27] points out the usual coexistence of scleromalacia perforans and rheumatoid arthritis. He believes that the choroid never bulges outward, and that the disease attacks only persons over 50. The author also differentiates this condition from necrotic nodular scleritis.

CORNEAL DISTURBANCES NOT ASSOCIATED WITH METABOLIC OR SYSTEMIC DISEASE

Obstetrical Lesions of the Cornea with Formation of Hyaline Cords in the Camera Anterior.—The subject has been carefully studied by Sörensen,[28] who reports a case of hyaline cords on the posterior surface of the cornea and in the

anterior chamber, as a result of delivery by means of forceps. He briefly summarizes the subject and divides the lesions etiologically into three groups: (1) those part of a congenital anomaly in which, in addition, there is a defective development of the iris, possibly because of fetal inflammation (Mann); (2) those in intraocular inflammations in adults, and (3) those following trauma. Lesions of the last groups are doubtless the commonest and are usually caused by the application of obstetrical forceps. The author's case no doubt fell into the last classification. Sörensen agrees with most authors that such injuries of the cornea are due to squeezing of the globe between the upper part of the orbit and the blade of the forceps and that the sudden increase of intraocular pressure during the delivery is capable of producing rents in Descemet's membrane. The cornea then becomes swollen and edematous, and this constitutes the initial opacity, which in milder forms subsides in the course of a few days. Descemet's membrane sometimes retracts, and indeed may be separated to a greater extent, so that it will be seen floating in the anterior chamber. The part that is denuded is again covered with endothelium, and a new Descemet membrane forms from this endothelium.

Balavoine [29] suggests another classification: (1) an acquired form, which would include the striae seen in buphthalmos, as well as those considered post-traumatic and postinflammatory, and (2) congenital malformation of the posterior corneal surface and of the anterior chamber. Microscopic examination of the hyaline network in one of his cases showed that the striae were formed by endothelial cells which had secreted a collagenous substance. The author suggests that the endothelial cells proliferate to form filaments, which anastomose in a fashion similar to that of the endothelial cells of the cornea in tissue cultures.

Terriens' Dystrophy.—Although nothing especially new has been reported regarding this disease during the past year, there are reports by Leibiger,[30] Legrand and Hervouet,[31] and Baron and Saba.[32] The last two authors treated a patient with large doses of thiamine and vitamin E, without improvement.

NEW DISEASES

Focal Scleral Necrosis.—Jones and Reese [33] report a hitherto undescribed late sequela of irradiation, namely, focal scleral necrosis. Radiation cataract, late skin changes, and effects on bone growth are well known. The less common sequela described presents a striking clinical appearance. Three cases are described, with a report of the pathological examination of one eye.

The necrosis found is analogous to that seen in bone necrosis following irradiation. The sequestration phenomenon may follow. Both gamma and beta radiations are demonstrated to be capable of producing scleral necrosis. It is pointed out that 18 and 4 years, respectively, elapsed after treatment with gamma radiation, while only 6 weeks passed between the initiation of beta radiation therapy and the appearance of an ulcer. The exact dosage is unknown, but in these cases a minimum of 1,500 rep, with the other factors unknown, was sufficient to produce the necrosis. This is a dose of beta rays considered moderate and commonly employed.

Moniliasis.—The first case in which Candida albicans was demonstrated in the cornea is reported by Mendelblatt.[34] It occurred in a 56-year-old white man who came to the hospital 12 days after the onset of the disease. A corneal ulcer was present, the scrapings from which showed the organisms with a Gram stain. The

ulcer rapidly became worse in spite of daily cauterizations with iodine and topical applications of every known antibiotic. Seventeen days after admission the ulcer perforated; the eye became blind and was enucleated. The pathological report, by F. Phinizy Calhoun Jr., described the yeast-like fungi throughout the cornea and a large hypopyon in the anterior chamber. The disease should be suspected in nonspecific granulomas and not confused with tuberculosis.

Zeissitis.—What appears to be a new clinical entity, called mycotic Zeissitis, is described by Vidal.[35] The disease is caused by secretions of the Pityrosporum. The fungus is round, and its clear sheath is made up of lipoproteins. During its growth it can invade the conjunctival sac and produce severe conjunctivitis and chronic keratitis. It is said to produce an allergic condition of the sac, which is aggravated by any surgical intervention. Mucin and lipotropic agents tend to arrest the development of the Pityrosporum.

UNUSUAL DISEASES

Scleredema Adultorum.—Breinin [36] reports a case of rare disease first described by Buschke (1900, 1902). One hundred cases have heretofore been reported. The disease is characterized by a generalized nonpitting edema. Ocular complications of edema of the lids and conjunctiva may persist after general manifestations are gone. A peculiar type of lymphangiectasia in the conjunctiva is described, associated with a secondary, trophic corneal disturbance (superficial punctate keratitis).

Heslin [37] reports a case in which the clinical and laboratory diagnosis was made eight years previously. All symptoms subsided within 15 months except for an unusual form of chemosis, which persisted. Puffiness of the lids was pronounced. Bilateral superficial punctate keratitis was present in the lower half of both corneas. The conjunctiva was notable for its solid-appearing, dead-white chemosis. With the slit lamp, interlacing, coiled, discrete, tube-like channels were seen to be superficially placed. Biopsy showed stromal edema of the conjunctiva and the presence of many small endothelium-lined tubules, around which were scattered clumps of lymphocytes.

In a discussion of this case, Breinin elaborated on the past and present-day concepts of the condition. He reported that treatment with hyaluronidase accomplished nothing and that cortisone made the condition worse.

Porokeratosis Mibelli with Corneal Participation.—This disease is described by Kiessling [38] in an 11-year-old child. The skin lesion was noted near the external canthus 10 years before. The eye gradually became involved, and gray opacities were noted in the adjacent corneal epithelium. Application of solid carbon dioxide and irradiation appeared to be successful in its treatment.

PTERYGIUM

A number of significant reports have been published during the past year on the subject of pterygium, including both medical and surgical forms of treatment. The most significant reports seem to be those of Carriker.§ During a two-year period 170 patients had surgical removal of pterygia at the Gorgas Hospital, in the Canal Zone. Eighteen per cent were American white persons. Fifteen per cent of these 170 patients had operations for recurrent pterygium. The author finds

§ References 39 and 40.

that improper nutrition is suggested as a possible etiologic factor, and that chronic conjunctival inflammations may favor the development and growth of the lesion. He advocates a definite surgical routine, with removal of episcleral tissue, leaving a bare scleral area, followed by the use of cortisone.

Carriker also has been interested in investigating a nonsurgical treatment for this disease. He has treated pterygia with local injections of 0.3 to 0.4 cc. of 1% procaine hydrochloride mixed with hyaluronidase. Forty patients with various stages of the disease were treated. He concludes that hyaluronidase injected into an early pterygium caused resolution of the growth if there was no more than 1-mm. progression of the apex onto the cornea. Hyaluronidase also hastened reabsorption of subconjunctical hemorrhages.

Rosenthal [41] reports on 77 patients with 85 pterygia, all treated by himself at Charity Hospital in New Orleans. Forty-two eyes were treated surgically, and 43, with beta radiation, delivered by a Swanberg 10-mc. applicator. In the surgical group, several were treated for recurrent pterygia. Surgical treatment failed in 15%, and beta radium therapy failed in 19%, percentages which are about the same. The author concludes that the McReynolds operation plus early postoperative use of the radium applicator is the best therapy for pterygium now available.

Pavišić [42] has made interesting keratometric measurements in 64 cases before and after surgery. In 70% operation was followed by an increase in curvature of the horizontal corneal meridian. It was thought that the pterygium had probably caused a flattening of the horizontal meridian.

EXAMINATION AIDS AND METHODS

Few new important methods of examination or aids to the ophthalmologist's fact-finding devices have come to the reviewer's attention this year.

Swan,[43] in reporting the use of 2% sodium carboxymethylcellulose in glycerin as a dehydrating agent, also discusses other methods of clearing corneal bedewing. He calls attention to the fact that permeability of the epithelium can be increased by a combination of physical and chemical means which allow fluid to escape. Topical anesthesia increases the permeability of the epithelium. It also condenses the precorneal film and therefore increases its osmotic pressure, a factor which favors removal of water from the epithelium. This condensation of the precorneal film results when the cornea and conjunctiva are anesthetized, because the lessened lacrimation and reduced blinking favor evaporation of fluid from the corneal surface. Further clearing can be effected by gentle massage of the cornea with a glass rod, as recommended by C. S. O'Brien.

Clearing can be hastened by instilling into the conjunctival sac a highly hydroscopic collyrium, such as glycerin, recommended by Cogan (1943). However, Swan calls attention to the irritation caused by glycerin, which increases tearing and therefore the amount of clearing.

The author recommends a dehydrating jelly made by adding 2 gm. of sodium carboxymethylcellulose to 100 cc. of glycerin U. S. P. It can be administered in a standard ophthalmic ointment tube. This jelly substance can be placed on the anesthetized cornea without spilling it over onto the conjunctiva. Clearing of the epithelium is evident in one minute. The clearing can be increased by spreading the jelly over the cornea with a glass rod, at the same time gently massaging the

epithelium. The degree and duration of the clearing are more marked than when glycerin is used alone. During two years the jelly has been administered to at least 200 patients, without ill-effects.

A method of measuring corneal thickness is reported by Paycha,[44] and the author points out the importance of determining this following the course of parenchymatous keratitis, and especially in determining the depth of the bed required for lamellar transplant. A corneal microscope with a micrometer eyepiece is used with a triangle formed by the beam from the lamp held at an angle of 71 degrees to the visual axis; the thickness can be calculated with an error of only 0.05 to 0.07 mm.

CHEMICAL BURNS OF THE EYE

The present-day concepts of the treatment of ocular burns, in the light of his own experimental and clinical experience, are carefully covered by Harley.[||] He reports experiments for the determination of the efficiency of calsulfhydryl in the treatment of burns caused by the following chemicals: hydrochloric acid, sodium hydroxide, maleic anhydride, acetic acid, iodoacetate, sulfuric acid, creosol, lactic acid, and calcium oxide. An attempt was made to produce a standard reproducible lesion of moderate severity in rabbits. The calsulfhydryl-treated eye was neither better nor worse than the control eye, in which no treatment was used. With only one chemical, iodoacetate, did calsulfhydryl, in three paired experiments, give consistently better results than those in the control eye. This is said to be in accord with its known enzyme-inhibiting properties and specific protein-denaturant qualities. The author advises caution in attempting to convert results in animal experiments to clinical evaluations in human subjects.

The technique of "denudation of the cornea" advocated by McLaughlin is said to have certain advantages, especially in alkali burns. Cortisone is recommended, as it appears to have value in inhibiting fibroblastic proliferation and corneal vascularization.

Harris and Cohen,[47] through rabbit experimentation, have investigated the effect of hyaluronidase on the severity of lewisite (β-chlorovinyl-2-chlorarsine) burns, and the authors found that it does not influence the treatment of these burns with dimercaprol U. S. P. (BAL).

Eareckson, Miller, and Long [48] report a case in which the diagnosis of corneal infection due to Pseudomonas aeruginosa was made in which treatment with polymyxin B and Varidase (streptokinase-streptodornase) was relatively successful. Infection of the cornea occurred after injury with a foreign body, which was removed three days after it was imbedded. An ulcer and ring abscess of the cornea followed two days after the removal of the foreign body. A culture yielded a pure growth of Ps. aeruginosa. Early treatment consisted of iodine cauterization and systemic and local administration of chloramphenicol and streptomycin. These medications did not help, and after the infection had spread to the entire cornea, the patient was given large doses of polymyxin B and an eye bath of Varidase, containing 20,000 units of streptokinase and 12,000 units of streptodornase. This combined treatment was effective, and the cornea cleared remarkably. The authors are of the opinion that thick mucopurulent exudates prevent effective antibiotic action and that Varidase is a tool for removing fibrin and pus.

|| References 45 and 46

Haselmann, Pulfrich, and Haselmann [49] point out that clinical and animal experiments suggest that topical application of pantothenic acid favors the regeneration and functional recovery of damaged corneal epithelium. They advise its use in recurrent erosions, trophic ulcers, superficial punctate keratitis, and dendritic keratitis after the virus has been destroyed with iodine.

Hallerman [50] notes that the corneal epithelium contains more acetylcholine than any other tissue and is supposed to have a protective function for the epithelium. However, the substance is quickly destroyed and must be instilled every two minutes. The author reports good results in five cases of lime or acid burns, but the results were equivocal in herpes corneae and in the dystrophies.

Klein and Millwood [51] describe a series of experiments in the treatment of Ps. aeruginosa infection using gelatin caps and discs impregnated with streptomycin. In glycerin discs 0.1 gm. of the drug, and in alginate caps 0.06 gm., was sufficient protection against massive experimental infection. Thus, it is said that in a proper vehicle, streptomycin in rather small doses can be effective. It is recommended that first-aid stations of industrial plants use this method in corneal lacerations and after removal of foreign bodies as an effective preventive. The subconjunctival injection of the larger doses in epinephrine solution is recommended for treatment of the established infection.

Calcified Corneal Opacities.—Grant [52] describes a new technique for the dissolution of calcified corneal opacities. These may result from exogenous causes, such as lime burn, or from endogenous causes, such as protracted uveitis, hypercalcemia, or phthisis bulbi. He employs a 0.01 M solution of the neutral sodium salt of ethylenediamine tetraacetic acid (EDTA). Removal of calcific deposits from the cornea may be indicated for improvement of vision or for relief of discomfort from particles which are extruding through the epithelium. When epithelium overlies the opacity, the epithelium must first be removed. The value of this treatment is well demonstrated by six case reports. EDTA is widely employed industrially under the trade names of Versene and Sequestrene for keeping calcium (and other metals) in solution in unreactive form. Solutions of the same substance have been used for the dissolution of calcific kidney stones and in the experimental treatment of lead poisoning.

Linhart [53] follows the treatment advised by Lindner for band-shaped keratopathy. He reports one patient with this disease whose vision was 20/100 and was improved to 20/20. The treatment consisted of light curettage of the cornea, after which it was dried with a cotton applicator and 2% hydrochloric acid solution was applied over the involved site by means of a wooden applicator tip. The gray, burned site was again gently curetted, and the eye was flushed with tetracaine (Pontocaine) and epinephrine. One week later the treatment was repeated.

Pines [54] has had an extensive experience in the treatment of trachoma and reports only 50% success with Denig's operation for pannus crassus. He advocates the subconjunctival injection of 0.1 to 0.2 cc. of 1% solution of ferric chloride close to the limbus. The injections are well tolerated, and the author states that five to six injections usually produce a cure.

An Iodine-Vapor Applicator for Treatment of Dendritic Keratitis.—Grant [55] describes and illustrates a small, convenient applicator for the treatment of herpes corneae with iodine vapor. Since he first described this treatment, the applicator has been used on 40 corneas. The applicator is made from a small glass-stoppered

test tube. Iodine crystals are contained in the closed end of the tube by a small wad of fiber glass. The open end of the tube is applied directly to the anesthetized cornea. The duration of the application depends upon the distance from the surface of the iodine crystals to the corneal surface. With a crystals-to-cornea distance of 16-20 mm., an effective dose is delivered in 3.5 minutes. The treatment is said to be more convenient than application or "scrubbing" with tincture of iodine. The discomfort following its application is about the same as when tincture of iodine is applied. The results appear to be equally good.

Effect of Locally Administered Heparin on the Eye.—Vannas [56] presents a monograph on this subject, which includes a short review of heparin. The observations were based on the local administration of heparin to the eye. Twenty test series were carried out on 184 rabbits and in 61 clinical cases. The rabbit's normal eye tolerated instillations of 30% sodium heparin solution well. It caused a slight reduction in the tension. Subconjunctival injection of 30% heparin sodium was followed by a strong chemosis, which persisted for 36 hours, a slight reduction in tension, and usually a slight miosis. Injected into the anterior chamber, heparin has a definite prolonging effect on the blood-clotting time, but the effect is considerably less than if administered directly into the blood. Heparin seemed to have a retarding effect on the course of panophthalmitis caused by injections of Staph. aureus into the anterior chamber. It also made milder the recovery period of iritis induced in rabbits by sensitization to horse serum.

Used in clinical iritis in humans, heparin treatment seemed to have a relieving effect on acute symptoms of iritis. The patient's subjective pains disappeared rapidly. The effect of heparin on primary glaucoma was not striking. It seems that the normal, as well as the diseased, eye tolerated heparin well. A man with chronic uveitis used heparin ointment many times daily during two months, and the vision improved. A boy with total blood staining of the cornea after a perforating wound used heparin drops every two hours during the day for three months. The blood staining almost completely disappeared.

CORTISONE AND HYDROCORTISONE IN TREATMENT OF CORNEAL DISEASE

Thygeson, Hogan, and Kimura [57] have carefully reviewed the role of cortisone in bacterial, as well as nonbacterial, keratitis. They give a complete review of the subject, including an extensive bibliography, and outline their own well-designed and well-controlled experiments. The article should be read in its entirety. The authors state that ample clinical evidence is now available to indicate that topical use of cortisone and hydrocortisone has great value in controlling certain important ocular diseases arising from bacterial allergies. Its usefulness has been definitely proved in phlyctenulosis, in nongramulomatous uveitis, and in marginal infiltrations or ulcers, with or without rosacea. A note of strong caution is sounded in regard to its use in primary infections, however. "Since the components of the inflammation act to limit infection, interference with inflammatory phenomena can well result in a masking effect which is sometimes disastrous." The authors believe its usefulness in herpes simplex is most questionable and cite four cases, those of Irvine, Reeh, and Frissell plus one of their own, in which herpes corneae went on to perforation when cortisone was used. Their clinical observations indicate a rapid control of all marginal ulcers in a series of 23 cases. Cortisone appeared to be

completely ineffective in two cases of Mooren's (rodent) ulcer. It influenced favorably each of 11 cases of phlyctenular keratitis. Their experiments in which cortisone was administered topically and systemically to guinea pigs in the treatment of corneal ulcers due to Staph. aureus, Diplococcus pneumoniae and Pseudomonas aeruginosa indicated that cortisone had no protective effect in any instance, nor did it appear to detract from or enhance the effect of antibiotic therapy in a parallel series of experimental ulcers.

Allen's¶ experience has been parallel to that of Thygeson, Hogan, and Kimura. He likewise reports disastrous results in three cases of dendritic keratitis treated with cortisone. In the first case the cornea became necrotic. In another the hormone seemed to cause an increase in the virulence of the infection, and in the third the cornea perforated and the eye was lost.

Leopold# brings forth another factor that should be considered if one is going to employ an antibiotic along with these hormones. He points out that streptomycin and other antibiotics penetrate poorly when administered systemically but when the eye is inflamed these antibiotics penetrate into infected tissues. Furthermore, it has been shown that cortisone will reduce the permeability of the inflamed eye. It might, therefore, interfere with the penetration of these antibiotics into the eye at just a time when it is desired.

Drews, Barton, and Mikkelsen [58] have an excellent article on the treatment of acute interstitial keratitis with topical use of cortisone. From their previous study of 90 patients treated at the Midwestern Medical Center, St. Louis, between 1944 and 1950, they conclude that penicillin used alone or in combination with arsenicals and bismuth has no significant effect upon the course of interstitial keratitis. This conclusion is in keeping with that of others.

The authors report their results of treatment of 18 patients of acute interstitial keratitis. These patients were all given large doses of penicillin in oil over a 12-day period following admission. In addition, they were treated by hourly instillations of 2.5% cortisone drops plus 2.5% cortisone ointment at night. Their patients were observed from 2 to 16 months. Pain and photophobia were usually relieved within 3 to 4 days, and circumcorneal redness cleared in 6 to 18 days. Active anterior uveitis disappeared in all but two cases in from one to six weeks, and there was progressive clearing of the cornea in all cases. The final visual acuity of 20/20 or better was obtained in 26 of 29 treated eyes. No patient who had continued topical therapy with cortisone once or twice a day had a recurrence. Three experienced a recurrence when cortisone was discontinued. In each case the recurrence was promptly controlled when treatment was resumed. They conclude that topical cortisone therapy has proved to be effective, inexpensive, safe, and simple to administer.

SURGERY

Peritoneum as a substitute for conjunctiva in plastic surgery appeared to be a very useful adjunct to reconstruction operations of the orbit according to Allen.[59] In one of his patients a graft of autogenous peritoneal mucosa, approximately 30 mm. in diameter, was placed over the bare cornea and adjacent conjunctiva after

¶ Allen, J. H., in discussion on Thygeson, Hogan, and Kimura.[57]

Leopold, I. H., in discussion on Thygeson, Hogan, and Kimura.[57]

a lamellar keratectomy. The graft healed nicely; only slight superficial vascularization of the cornea recurred four months after surgery, and the patient was thereby prepared for a full-thickness corneal graft.

Egg membrane for chemical injuries of the eye has been used by Croll and Croll.[60] The authors feel that the delayed corneal healing that is commonly seen in chemical eye injuries is largely the result of continuous contact with the burned conjunctiva. The present knowledge of the subject is well reviewed, and the pathology of burns, particularly lime burns, is carefully described and well illustrated. The authors are strong advocates of the use of boiled egg membrane to cover the cornea and to separate the injured opposing conjunctival surfaces. Their careful technique of applying membrane to cover the cornea and bulbar conjunctiva is described. After meticulous and careful irrigation, a double layer of egg membrane is sewed in place. A double eye bandage is applied; the first dressing is done in 72 hours, but the membranes are not removed until the 6th day, when the sutures are also removed.

Twenty-six patients were treated, with excellent results. The authors agree with O'Connor and others, who advocate immediate grafting in burns of the eye because early epithelization of the conjunctiva seemed to be of prime importance.

An experimental study of plastic material as replacement for the cornea is reported by Stone and Herbert.[61] The report is a preliminary one on work started several years ago. An attempt has been made to place an interlamellar plastic disc in a rabbit's cornea to observe how well it might be tolerated. After this the corneal substance anterior to the disc is excised. A method has been devised for the fixation of artificial implants in the rabbit cornea by means of a fabrication of the periphery of the implant to permit firm ingrowth of the corneal tissue. Interlamellar implants have been well tolerated, with little reaction for a period of 24 months. An incompletely covered interlamellar disc, that is, with the anterior surface removed, remained in place in one rabbit's cornea for 12 months. The authors believe that it is still too early for human experimentation, but are next graduating to monkeys, which they hope will tolerate the plastic implants for a longer period.

KERATOPLASTY

The literature on keratoplasty and allied subjects continues to occupy a large portion of the total literature on the cornea. Reports on small groups of cases appear from all over the world, and in general the results have not shown any striking improvement over those previously reported. It is my impression that lamellar keratoplasty is occupying a position of greater prominence than heretofore (Kwaskowski [62]).

Stored Corneas.—Abreu Fialho [63] reviews some of the work done at the cornea bank of the Santa Casas de Misericordia Hospital. In order to reduce clouding and to facilitate the obtaining of lamellar grafts, the posterior two-thirds of the globe is imbedded in paraffin and kept at a temperature of 4 C. For perforating grafts, the isolated cornea is kept in paraffin in the refrigerator. Isolated cornea suspended in the refrigerator showed a loss of weight of from 15 to 20% in two hours and from 64 to 78% in 24 hours, due to dehydration. Immersing severely dehydrated corneas in Ringer's solution for 24 hours produced a hydration of the cornea to, and frequently in excess of, the initial weight.

The dangers occurring from the tissues themselves in stored corneas and their influence on the postoperative course of keratoplasty are pointed out by Orzalesi and Ciuffo.[64] They review the causes of clouding of corneal transplants. In tissue extracts prepared from corneas stored in different media for varying periods, the authors have found a histamine-like substance that causes increased capillary permeability and leucocytic exudation. The effect of this substance is to some extent inhibited by cortisone. The authors believe that the pathologic changes occurring in corneal grafts are probably due to allergic reactions between graft and host.

Heterografts.—An interesting report of successful lamellar heteroplasty is reported by Choyce.[65] Lamellar grafts of human and cat corneas were transplanted into rabbits. The center of the host cornea was removed to Descemet's membrane, and a linear-shaped transplant was inserted intracorneally. All the grafts remained clear for two years, and the author believes that they would have remained so indefinitely.

Technique and Instruments.—Friede,[66] in doing penetrating keratoplasty, advises trephining down to Descemet's membrane. This membrane is then excised, leaving a marginal shelf. The author believes that this gives better protection against the aqueous at the border.

Gerkowicz [67] has described a modification of Filatov's trephine. Essentially it contains a small hook which holds the transplant, and thus pressure on the globe and stripping of Descemet's membrane are avoided.

Effect of Cortisone, Paraaminobenzoic Acid and Histidine.—The effect of cortisone in experimental homologous keratoplasty has been carefully studied in the rabbit by Ojers, Yasuna, and Scheie.[68] These authors draw the following conclusions from their researches on this subject: 1. The ocular reaction following keratoplasty in rabbit eyes is consequent to the operative trauma rather than to allergy to homologous tissue. 2. Cortisone decreases the duration and severity of the ocular reaction to keratoplasty in rabbit eyes. 3. Corneal neovascularization appeared to be inhibited when systemic cortisone therapy was started on the day of surgery. 4. Postoperative iridocyclitis was reduced in amount and duration by systemic use of cortisone. 5. The percentage of clear corneal grafts was increased in those rabbits receiving cortisone postoperatively.

The action of paraaminobenzoic acid, histidine, and cortisone on corneal transplants was similarly studied by Borioni and Scassellati-Sforzolini.[69] These authors subjected rabbits to corneal trephining. Symmetrical perforating operations were done on the two eyes. In some the discs were replaced; others received transplants from the opposite eye. One series of nine animals were given instillations of 10% paraaminobenzoic acid (PABA) solution in the conjunctiva four times daily. A second series of nine were given 5% histidine ointment twice daily, and a third series, a 1% cortisone solution four times daily. All animals were given penicillin intramuscularly. Only one eye was treated. The fellow eye was considered the control. In four animals treated with PABA the transplant remained clear for at least two months. In two the transplant became opaque. All eyes treated with histidine ointment retained a clear graft for two months. The corneas treated with cortisone either showed complete opacification (2 animals, which were rejected) or became necrotic. In all controls, transplantation failed. The author stresses the therapeutic possibilities of PABA and histidine.

Lamellar Corneal Grafts.—The indications for full-thickness graft, as well as lamellar grafts, are carefully described by Rycroft and Romanes.[70] They point out that half-thickness grafts can be made to cover an area of scar up to 10 mm. in diameter, while a 6-mm. perforating graft is of optimal size. Lamellar grafting exposes the eye to less risk and requires less skill. Clouding of the graft occurs less often in the lamellar type and, when it occurs, is an allergic reaction, which is unpredictable but can probably be avoided, or at least lessened, by the routine postoperative use of antihistaminics. The authors use the technique of Paufique. Egg membrane is sutured over the cornea, and the dressing is not disturbed for one week. Cortisone drops are used every hour after the eighth day. Sixty-two consecutive cases are described, with generally satisfactory results.

SUPPLEMENT

Many excellent review articles have been cited extensively on the foregoing analysis of the last year's literature on the cornea and sclera. An attempt has been made to carry on the recent advances in our knowledge of corneal and scleral disease from where Berliner* left off, in his splendid monographs. It might be well, however, to mention a few authors and the subject matter which they have treated.

Piper [73] has given an excellent review of external diseases of the eye and their sequelae. The ocular manifestations of the dermatoses and the associated eye and skin manifestations of systemic diseases have been well summarized by Thygeson,[74] Givner,[75] and Allende.[76] Similarly, ocular allergy, with special reference to its pathologic findings, and its diagnosis and treatment have been recorded by Payne,[77] Hanser,[78] and Ruedemann.[79]

The familial nodular dystrophies have been thoroughly summarized and reviewed by François,[80] and Borsello [81] gives an excellent bibliography on this subject. Katz,[82] again, has reviewed our knowledge of Salzmann's nodular dystrophy, though little new is offered with reference to its etiology or treatment. Finally, a detailed survey of the older literature on pterygium and its surgery is written by Toth [83] an article which is well worth reading for anyone who is especially interested in this subject.

* References 71 and 72.

REFERENCES

1. Irvine, A. R., and Irvine, A. R., Jr.: Variations in Normal Human Corneal Endothelium: A Preliminary Report of Pathologic Human Corneal Endothelium: Am. J. Ophth. **36**:1279-1285, 1953.

2. Teng, C. C., and Katzin, H. M.: The Basement Membrane of Corneal Epithelium: A Preliminary Report, Am. J. Ophth. **36**:895-900, 1953.

3. Aurell, G., and Holmgren, H.: On the Metachromatic Staining of the Corneal Tissues and Some Observations on Its Transparency, Acta ophth. **31**:1-27, 1953.

4. Smelser, G. K., and Ozanics, V.: Structural Changes in Corneas of Guinea Pigs After Wearing Contact Lenses, A. M. A. Arch. Ophth. **49**:335-340, 1953.

5. Bock, R. H., and Maumenee, A. E.: Corneal Fluid Metabolism: Experiments and Observations, A. M. A. Arch. Ophth. **50**:282-285, 1953.

6. Potts, A. M.: The Nutritional Supply of Corneal Regions in Experimental Animals: II. The Problem of Corneal Transparency and the Tonicity of Tears, Am. J. Ophth. **36**:127-138 (June, Pt. 2) 1953.

7. Fedukowicz, H., and Horwich, H.: The Gram-Negative Diplobacillus in Hypopyon Keratitis, A. M. A. Arch. Ophth. **49**:202-211 (Feb.) 1953.

8. Bambert, W.: Etiology and Treatment of Ulcus Corneae Serpens, Klin. Monatsbl. Augenh. **121**:271-283, 1952.

9. Belmonte-Gonzalez, N.: A Study of the Aqueous Humor in Traumatic Ulcers of the Cornea, Arch. Soc. oftal. hispano-am. **12**:598-603, 1952.

10. Oksala, A.: Interstitial Keratitis and Chorioretinitis, Acta ophth. **30**:437-441, 1952.

11. Oksala, A.: Studies on Interstitial Keratitis Associated with Congenital Syphilis Occurring in Finland, Acta ophth., Supp. 38, 1952.

12. Thygeson, P.: Herpes Corneae, Am. J. Ophth. **36**:269-270, 1953.

13. Braley, A. E.: Experimental Herpes Simplex, Am. J. Ophth. **35**:1737-1747, 1952.

14. Rossetti, D., and Borio, G.: Cause and Pathogenesis of Ocular Herpetic Manifestations, Arch. ottal. **56**:337-398, 1952.

15. Arakawa, S.; Ohashi, T.; Seki, T.; Kitamura, O.; Sakurababyashi, H., and Goto, H.: Experimental Study of Epidemic Keratoconjunctivitis, Acta Soc. ophth. jap. **56**:367-371, 1952.

16. Pillat, A.: Epidemic Keratoconjunctivitis (1938) in Vienna, Wien. klin. Wchnschr. **65**:41-43, 1953.

17. Braley, A. E., and Alexander, R. C.: Superficial Punctate Keratitis: Isolation of a Virus, A. M. A. Arch. Ophth. **50**:147-154, 1953.

18. Brœndstrup, P.: Infantile Cystinosis, with Cystine Crystals in Cornea and Conjunctiva, Acta ophth. **30**:365-377, 1952.

19. Ruedemann, A. D., Jr.: Osteogenesis Imperfecta Congenita and Blue Sclerotics: Clinicopathologic Study, A. M. A. Arch. Ophth. **49**:6-16, 1953.

20. Goar, E. L., and Smith, L. S.: Polyarteritis Nodosa of the Eye, Am. J. Ophth. **35**:1619-1625, 1952.

21. McWilliams, J. R.: Ocular Findings in Gout, Am. J. Ophth. **35**:1778-1783, 1952.

22. Hogan, M. J.: Atopic Keratoconjunctivitis, Am. J. Ophth. **36**:937-947 (July, Pt. 1) 1953.

23. Barnes, H. D., and Boshoff, P. H.: Ocular Lesions in Patients with Porphyria, A. M. A. Arch. Ophth. **48**:567-580, 1952.

24. Soudakoff, P. S., and Whalman, H. F.: Ocular Pemphigus: Report of a Case with the Histologic Findings in the Cornea, Am. J. Ophth. **36**:231-236, 1953.

25. Kratka, W. H.: Episcleritis and Erythema Nodosum: A Collagen Syndrome, Case Report, Am. J. Ophth. **36**:510-513, 1953.

26. Boehringer, H. R.: Scleromalacia as a Symptom of Severe Sepsis, Klin. Monatsbl. Augenh. **121**:473-479, 1952.

27. François, J.: Scleromalacia Perforans, Arthritis Deformans and Pemphigus, Tr. Ophth. Soc. U. Kingdom **71**:61-72, 1951.

28. Sörensen, C. H. R.: Obstetric Lesions of the Cornea with Formation of Hyaline Cords in the Camera Anterior, Acta ophth. **30**:223-227, 1952.

29. Balavoine, E.: Acquired Retrocorneal Hyaline Formation, Ann. ocul. **186**:11-140, 1953.

30. Leibiger, W.: A Progressing Corneal Ulcer Forming a Furrow, Klin. Monatsbl. Augenh. **121**:587-589, 1952.

31. Legrand, J., and Hervouet, F.: Marginal Ectasia of the Cornea (Terrien's Disease), Ann. ocul. **186**:97-110, 1953.

32. Baron, H. G., and Saba, J.: Terrien's Disease, Arch. oftal. Buenos Aires **27**:116-120, 1952.

33. Jones, I. S., and Reese, A. B.: Focal Scleral Necrosis: A Late Sequel of Irradiation, A. M. A. Arch. Ophth. **49**:633-636, 1953.

34. Mendelblatt, D. L.: Moniliasis: A Review and a Report of the First Case Demonstrating the Candida Albicans in the Cornea, Am. J. Ophth. **36**:379-385, 1953.

35. Vidal, F.: Zeissitis Caused by the Round Pityrosporum, Arch. oftal. Buenos Aires **27**:358-363, 1952.

36. Breinin, G. M.: Scleredema Adultorum: Ocular Manifestations, A. M. A. Arch. Ophth. **50**:155-162, 1953.

37. Heslin, T.: Sclererderma Adultorum: Ocular Manifestations, A. M. A. Arch. Ophth. **48**:521-523, 1952.

38. Kiessling, W.: Porokeratosis Mibelli with Corneal Participation, Dermat. Wchnschr. **49**:1168-1170, 1952.

39. Shreck, H. W., and Carriker, F. R.: Pterygium Problems in the Canal Zone, A. M. A. Arch. Ophth. **48**:716-719, 1952.

40. Carriker, F. R.: The Use of Hyaluronidase in Ophthalmology, Am. J. Ophth. **35**:1765-1768, 1952.

41. Rosenthal, J. W.: Beta-Radiation Therapy of Pterygium, A. M. A. Arch. Ophth. **49**:17-23, 1953.

42. Pavišić, Z.: Refraction and Corneal Astigmatism in Cases of Pterygium, Ophthalmologica **124**:157-165, 1952.

43. Swan, K. C.: A Dehydrating Jelly to Clear Corneal Bedewing, A. M. A. Arch. Ophth. **50**:75-78, 1953.

44. Paycha, F. C.: Method of Measuring Corneal Thickness, Arch. opht. **13**:156-158, 1953.

45. Harley, R. D.: An Experimental Study on the Evaluation of Hydrosulphosol in the Treatment of Ocular Injuries Due to Chemical Burns, Am. J. Ophth. **35**:1653-1675, 1952.

46. Harley, R. D.: Treatment of Chemical Burns of the Eye, A. M. A. Arch. Ophth. **49**:413-418, 1953.

47. Harris, C., and Cohen, B. S.: Effect of Hyaluronidase on the Therapeutic Efficacy of BAL Applied to Rabbit Cornea, Am. J. Ophth. **36**:777-781, 1953.

48. Eareckson, V. O., Jr.; Miller, J. M., and Long, P. H.: Infection of Eye Due to Pseudomonas Aeruginosa Treated with Polymyxins B and "Varidase," A. M. A. Arch. Ophth. **49**:158-160, 1953.

49. Haselmann, G.; Pulfrich, K., and Haselmann, H.: The Treatment of Corneal Epithelial Damage with Pantothenic Acid, Ophthalmologica **123**:357-364, 1952.

50. Hallerman, W.: The Topical Administration of Acetylcholine, Klin. Monatsbl. Augenh. **121**:397-408, 1952.

51. Klein, M., and Millwood, E. G.: Control of Experimental Corneal Infection with Medicated Semi-Solid Contact Cap and Disk, Brit. J. Ophth. **37**:30-36, 1953.

52. Grant, W. M.: New Treatment for Calcific Corneal Opacities, A. M. A. Arch. Ophth. **48**:681-685, 1952.

53. Linhart, R. W.: Treatment of Calcareous Film of the Cornea, Am. J. Ophth. **35**:1497-1498, 1952.

54. Pines, N.: Treatment of Pannus Crassus, Rev. internat. du trachome **36**:116-119, 1953.

55. Grant, W. M.: An Iodine-Vapor Applicator for Treatment of Dendritic Keratitis, A. M. A. Arch. Ophth. **48**:749-751, 1952.

56. Vannas, S.: Experimental and Clinical Investigations into the Effect of Locally Administered Heparin on the Eye, Acta ophth., Supp. 40, 1952.

57. Thygeson, P.; Hogan, M. J., and Kimura, S. J.: Cortisone and Hydrocortisone in Ocular Infections, Tr. Am. Acad. Ophth. **57**:64-85, 1953.

58. Drews, L. C.; Barton, G. D., and Mikkelsen, W. M.: The Treatment of Acute Syphilitic Interstitial Keratitis with Topical Cortisone, Am. J. Ophth. **36**:90-103, 1953.

59. Allen, J. H.: The Use of Peritoneum as a Substitute for Conjunctiva in Plastic Surgery: Preliminary Report, Am. J. Ophth. **36**:1249-1252, 1953.

60. Croll, M., and Croll, L. J.: Egg Membrane for Chemical Injuries of the Eye, Am. J. Ophth. **35**:1585-1596, 1952.

61. Stone, W., Jr., and Herbert, E.: Experimental Study of Plastic Material as Replacement for the Cornea: A Preliminary Report, Am. J. Ophth. **36**:168-173 (June, Pt. 2) 1953.

62. Kwaskowski, A.: Corneal Transplants in the Eye Clinic in Lodz, Klin. oczna **22**:127-136, 1952.

63. Abreu Fialho, S.: Characteristics of the Cadaver Cornea, Rev. brasil. oftal. **10**:315-319, 1952.

64. Orzalesi, F., and Ciuffo, P.: Tissue Changes Occurring in Corneas During Storage and Their Probable Influence upon the Postoperative Course of Keratoplasty, Ophthalmologica **125**:91-111, 1953.

65. Choyce, D. P.: Successful Transplantation of Human and Cat Corneal Tissue into Rabbit Corneae, Brit. J. Ophth. **36**:537-542, 1952.

66. Friede, R.: Penetrating Keratoplasty with a Descemet Margin, Klin. Monatsbl. Augenh. **121**:692-696, 1952.

67. Gerkowicz, K.: Modification of a Manual Trephine for Corneal Transplants, Klin. oczna **22**:239-242, 1952.

68. Ojers, G. W.; Yasuna, J. M., and Scheie, H. G.: Cortisone in Experimental Homologous Keratoplasty in the Rabbit, Am. J. Ophth. **36**:120-125 (June, Pt. 2) 1953.

69. Borioni, D., and Scassellati-Sforzolini, G.: Action of Paraaminobenzoic Acid, Histidine, and Cortisone on the Success of Corneal Transplants, Boll. ocul. **31**:623-631, 1952.

70. Rycroft, B. W., and Romanes, G. J.: Lamellar Corneal Grafts, Brit. J. Ophth. **36**:337-351, 1952.

71. Berliner, M. L.: Cornea and Sclera: Review of Literature, A. M. A. Arch. Ophth. **47**:250-267, 1952.

72. Berliner, M. L.: Cornea and Sclera: Review of Literature, A. M. A. Arch. Ophth. **49**:222-236, 1953.

73. Piper, H. G.: External Disease of the Eye and Their Sequelae, Klin. Monatsbl. Augenh. **122**:129-141, 1953.

74. Thygeson, P.: Ocular Manifestations of the Dermatoses, Tr. Am. Acad. Ophth. **56**:737-750, 1952.

75. Givner, I.: Associated Eye and Skin Manifestations of Systemic Disease, Tr. Am. Acad. Ophth. **56**:751-780, 1952.

76. Allende, M. F.: Dermatologic Relationships in Ophthalmology, Tr. Am. Acad. Ophth. **56**:781-790, 1952.

77. Payne, B. F.: Pathologic Findings in Allergic Diseases of the Eye, Tr. Am. Acad. Ophth. **57**:468-470, 1953.

78. Hanser, S. A.: Diagnosis and Treatment in Ocular Allergy, Tr. Am. Acad. Ophth. **57**:476-481, 1953.

79. Ruedemann, A. D.: Allergy of the Cornea and Bulbar Conjunctiva, Tr. Am. Acad. Ophth. **57**:471-475, 1953.

80. François, J.: Heredofamilial Corneal Dystrophies, J. genet. humaine **1**:103-138, 1952.

81. Borsello, G.: Familial Reticular Dystrophy of the Cornea, Rass. ital. ottal. **21**:272-289, 1952.

82. Katz, D.: Salzmann's Nodular Corneal Dystrophy, Acta ophth. **31**:377-383, 1953.

83. Toth, Z.: The Pterygium and Its Surgery, Klin. Monatsbl. Augenh. **122**:307-333, 1953.

BIBLIOGRAPHY

References not included in this bibliography are cited in the text.

Abel, H.: Topical Cortisone in Eye Disease, Acta ophth. **30**:47-52, 1952.

Alagna, G.: Influence of Vitamin B_{12} on the Healing of Corneal Wounds, Arch. ottal. **54**:77-88 (May-Aug.) 1950.

Angelone, L.: Chloramphenicol in the Treatment of Herpetic Disease of the Cornea, Rass. ital. ottal. **21**:513-536, 1952.

Ashton, N., and Hobbs, H. E.: Effect of Cortisone on Rheumatoid Nodules of the Sclera (Scleromalacia Perforans), Brit. J. Ophth. **36**:373-384 (July) 1952.

Babel, J., and Bourquin, J. B.: Experimental Research with Corneal Heterografts, Brit. J. Ophth. **36**:529-536 (Oct.) 1952.

Beckett, H. C.: Bilateral Congenital Anterior Staphyloma Treated by Keratoplasty, M. J. Australia **1**:372-373 (March 14) 1953.

Berens, C.: Corneal Transplantation: Special Plastic Moist Chamber for Donor Eye, A. M. A. Arch. Ophth. **48**:634-635 (Nov.) 1952.

Boudet, C.: Study of Vascularization After Keratotomy, Arch. opht. **12**:510-515, 1952.

Brand, I.: Metastatic Furunculiform Episcleritis, Klin. Monatsbl. Augenh. **120**:393-396, 1952.

Bruna, F.: More About Fehr's Corneal Dystrophy, Boll. ocul. **32**:74-80 (Feb.) 1953.

Chinaglia, V.: Marginal Degeneration of the Cornea: Clinical and Histological Contribution, Ann. ottal. e clin. ocul. **78**:497-526 (July) 1952.

Cohen, I. J.: Foreign-Body Abrasions of the Cornea, Acting as Concave Lens, Am. J. Ophth. **36**:981-982 (July, Pt. 1) 1953.

Contino, F.: Ocular Manifestations During the Course of Stevens-Johnson Disease, Riv. ital. trac. e pat. ocul. esot. **4**:5-17 (Jan.-March) 1952.

Daily, L., Jr., and Daily, R. K.: Transparent Transplant and Good Vision, After Loss of Lens in Keratoplasty, Am. J. Ophth. **36**:513-514 (April) 1953.

Technique of Corneal Transplantation, ibid. **36**:813-822 (June, Pt. 1) 1953.

de Leonibus, F.: Thickness of the Cornea in Eyes with Iridocyclitis, Rass. ital. ottal. **21**:407-414 (Nov.-Dec.) 1952.

de Vincentiis, M.: Bilateral Symmetrical Dystrophy of Bowman's Membrane: Report of a Case, A. M. A. Arch. Ophth. **48**:636-638 (Nov.) 1952.

Diener, F.: Acquired Keratoglobus, Klin. Monatsbl. Augenh. **121**:82-84, 1952.

Donahue, H. C.: Congenital Ectasia of the Cornea, A. M. A. Arch. Ophth. **48**:154-160 (Aug.) 1952.

François, J., and Rabaey, M.: Examination of the Cornea with the Phase-Contrast Microscope, Am. J. Ophth. **36**:799-802 (June, Pt. 1) 1953.

Frenandez-Repeto, S.: Double Pterygia, Arch. Soc. oftal. hispano-am. **12**:1310-1316 (Nov.) 1952.

Friede, R.: Repeated Keratoplasty, Klin. Monatsbl. Augenh. **121**:134-139, 1952.

Friedman, M. W., and Wright, E. S.: The Surgical Treatment of Ocular Pemphigus, Am. J. Ophth. **36**:237-240 (Feb.) 1953.

Gandolfi, C.: Conjunctival Pemphigus, Arch. ottal. **56**:133-141 (March-April) 1952.

Gezurian, Z. L.: The Infectious Agent in Sjögren's Syndrome, Arch. oftal. Buenos Aires **27**:265-267 (June) 1952.

Gross, G.: Treatment of Herpetic Keratitis with Dihydroargotamine, Klin. Monatsbl. Augenh. **121**:15-24, 1952.

Guenther: Treatment of Xerosis After Pemphigus, Klin. Monatsbl. Augenh. **120**:306-310, 1952.

Illig, K. M.: Use of Digestive Enzymes in Treatment of Corneal Disease, Klin. Monatsbl. Augenh. **120**:403-407, 1952.

Jaensch, P. A.: Virus Keratitis, Deutsche med. Wchnschr. **78**:428-431 (March 27) 1953.

Kazdan, L.: Repair of a Corneal Fistula with Ocular Muscle Tendon, Canad. M. A. J. **67**:472 (Nov.) 1952.

Kojima, K.; Niwa, Y.; Inamie, E., and Yoshino, M.: Ocular Symptoms of Epidermolysis Bullosa Dystrophica, Acta Soc. ophth. jap. **57**:163-165 (March) 1953.

Laval, J.: Use of Hydrocortisone (Hydrocortone) Acetate in Ophthalmology, A. M. A. Arch. Ophth. **50**:299-302 (Sept.) 1953.

Lemmingson, W.: Participation of the Eye in Bullous Epidermolysis, Klin. Monatsbl. Augenh. **122**:350-353, 1953.

Lepri, G.: Investigations of the Adrenal Cortex Function and of ACTH and Ascorbic Acid Therapy in Rosacea Keratitis, Arch. ottal. **54**:109-134 (May-Aug.) 1950.

Lister, A.: Malignant Pigmented Tumours in the Neighborhood of the Limbus Treated by Radical Excision Followed by Corneo-Scleral Graft: Report of 3 Cases, Tr. Ophth. Soc. U. Kingdom **71**:97-107, 1951.

Madroszkiewicz, M.: Treatment of Herpes of the Cornea with Chlortetracycline (Aureomycin), Klin. oczna **22**:243-245, 1945.

Malbrán, J. L.: Nonperforating Keratoplasty, Arch. oftal. Buenos Aires **27**:281-291 (July) 1952.

. and Cremona, A. C.: Corneoconjunctival Plastic with Fascia Lata, ibid. **27**:462-472 (Oct.) 1952.

Marconcini, E. A.: A Case of Perforating Scleritis, Gior. ital. oftal. **5**:442-451 (Sept.-Oct.) 1952.

Nañagas, P. J.: Nutritional Dystrophy of Corneal Epithelium: Preliminary Report of Patients Reacting Favorably to Vitamin Therapy, A. M. A. Arch. Ophth. **49**:536-552 (May) 1953.

Neame, H.: Oedema of the Cornea: The Importance of the Distinction Between Oedema of the Epithelium and of the Substantia Propria, Tr. Ophth. Soc. U. Kingdom **71**:381-389, 1951.

Nonnemacher, H.: Treatment of Progressive Scleroperikeratitis, Klin. Monatsbl. Augenh. **121**:707-712, 1952.

Oeri, J. J.: Problem of Noncoagulation of Blood in the Anterior Chamber, Acta ophth. **30**:181-202, 1953.

Paéz-Allende, F. S.: Two Cases of Anterior Gigantophthalmia (Megalocornea), Arch. oftal. Buenos Aires **26**:17-29 (Jan.) 1952.

Pinto, S.: Perforating Keratoplasty: Some Experimental Facts, Arq. portug. oftal. **4**:29-50, 1952.

Raimondo, N., and Leo, F.: Pathogenesis of Parenchymatous Keratitis on the Basis of Results Obtained with Local Cortisone Therapy, Ann. ottal. e clin. ocul. **78**:861-874 (Oct.) 1952.

Rama, G.: Ulcus Rodens: Etiopathogenesis and Therapy, Arch. ottal. **56**:157-174 (March-April) 1952.

Riehm, W.: Nonspecific Irritation in the Pathogenesis of Phlyctenular Inflammation, Klin. Monatsbl. Augenh. **122**:292-296, 1953.

Rio Cabanas, J. L.: Present Status of Pterygium Surgery, Arch. Soc. oftal. hispano-am. **12**:1298-1309 (Nov.) 1952.

Rosenthal, J. W.: The Blaskovicz Pterygium Operation, Am. J. Ophth. **36**:259-260 (Feb.) 1953.

Rumpelhardt, K.: Relationship Between Myopia and Corneal Scars, Klin. Monatsbl. Augenh. **120**:397-403, 1952.

Säkić, D.: Serpiginous Corneal Ulcer and Its Treatment by Catholysis, Ann. ocul. **185**:618-631 (July) 1952.

Salomaa, S., and Swanljung, H.: Clinical Experiences with ACTH and Cortisone in Eye Diseases, Acta ophth. **30**:53-58, 1952.

Salleras, A.: Total Penetrating Keratoplasty with Phacoerisis, Arch. oftal. Buenos Aires **27**:525-531 (Dec.) 1952.

Schneider, R.: Keratitis Pustuliformis Profunda, Wien. klin. Wchnschr. **64**:949 (Dec.) 1952.

Scuderi, G.: Chlortetracycline (Aureomycin), Chloramphenicol, and Oxytetracycline (Terramycin) in Corneal Herpes, Gior. ital. oftal. **5**:119-136 (March-April) 1952.

Sobanski, J.: Treatment of Scrofulous Inflammation of the Conjunctiva and the Cornea, Klin. oczna **22**:141-146, 1952.

Stanković, M.: A Case of Double Kayser-Fleischer Ring, Ophthalmologica **124**:100-104 (Aug.) 1952.

Szillinsky, R.: Closure of a Corneal Defect by Coagulation, Klin. Monatsbl. Augenh. **121**:78-79, 1952.

Tano, Y.: An Epidemic of Keratitis Disciformis in the Banshu District, Acta Soc. ophth. jap. **57**:288-295 (June) 1953.

Theobald, G. D., and Wilder, H. L.: Heerfordt's Syndrome, Tr. Am. Acad. Ophth. **57**:332-333 (May-June) 1953.

Tosi, B.: The White Rings of Coats, Arch. oftal. Buenos Aires **27**:222-228 (May) 1952.

Trautmann, I.: Megalocornea and Buphthalmos, Klin. Monatsbl. Augenh. **121**:539-543, 1952.

Velhagen, K., Jr.: Argyrosis of the Cornea, Klin. Monatsbl. Augenh. **122**:36-42, 1953.

Vrabec, F.: Histologic Study of Psoriasis of the Conjunctiva and Cornea: Case, Ophthalmologica **124**:105-108 (Aug.) 1952.

Wagner, F.: Bilateral Keratoplasty in Macular Corneal Dystrophy, Klin. Monatsbl. Augenh. **122**:261-272, 1953.

Weekers, L.: Changes in the Cornea Due to Local Medication with Sulfonamides and Antibiotics, Ann. ocul. **185**:549-551 (June) 1952.

Wilson, F. M., and Wilson, J. W.: Radioactive Strontium Therapy of the Eye: Corneal Biostandardization and Evaluation of an Applicator for Use in Ophthalmology, A. M. A. Arch. Ophth. **48**:686-695 (Dec.) 1952.

Yoruish, N. B.: Extensive Corneal Erosion Due to Shaving Lotion, Am. J. Ophth. **35**:1694-1695 (Nov.) 1952.

Correspondence

DIABETIC RETINOPATHY

To the Editor:—Under ordinary circumstances, we feel that medical controversy is wasteful of time and effort of the participants, since the situation is often cleared with the passage of time. However, the article by Bedrossian and others (A. M. A. Arch. Ophth. **50:** 277 [Sept.] 1953) and the accompanying editorial by F. H. Adler in the same issue, page 275, impels us to write this letter.

The theme of the editorial is the publication of misleading information, and the extravagant praise of the accompanying article by Bedrossian, which refutes our work (*Am. J. Ophth.* **34:** 613, 1951). We feel that a careful study of Dr. Bedrossian's own tables and method of procedure would make an unbiased observer come to a very different conclusion than did Dr. Bedrossian. Also, we should like to point out why Bedrossian's paper is not the ideal model that it is stated to be.

Our work (*Am. J. Ophth.* **34:** 613, 1951) was definitely a preliminary report and was so stated to be in the article. A refutation should not be a preliminary report, but the investigation should be of sufficient duration and carry sufficient weight to definitely disprove the earlier paper.

In order to refute our findings, the working classification adopted should have been similar to ours, so that definite claims could be refuted. Instead, an entirely different grouping was made, which is so artificial we do not believe that it would be workable. For example, if the number of hemorrhages in the retina were reduced from 10 to 1, which we feel would be a definite improvement, this would be classified as no improvement by Bedrossian. If the number of hemorrhages were reduced from 19 to 1, it would be only a slight improvement according to Bedrossian.

Dr. Bedrossian used a male-female hormone ratio of 50: 2.5 mg. In this formula the male-female hormone values actually cancel each other out, so that only the anabolic effect of these hormones remains. We use a 50:1 combination so as to get the effect of testosterone and yet neutralize some of its sexual side-actions. Thus Dr. Bedrossian did not use the same proportion of the hormones that we did.

Now, in regard to his method of control observations: Dr. Bedrossian's method of using saline and hormone in alternate cases sounds as though this were the ideal method. Practically speaking, it is almost impossible to compare exactly similar cases on an alternate basis, because they are impossible to obtain and, even more so, because the disease progresses at a different rate in different patients. A system whereby each patient acts as his own control is, we believe, often the better method. Our patients each had rutin, maximum diabetic control, and vitamin C by mouth and by injection without effect before hormone therapy was instituted. Thus our patients were also controlled. Those treated had responded to no previous therapy and exhibited a persistent progression of the disease or no periods of remission.

Now as to functional improvement without obvious objective improvement, which both the editorial and the article mention. If the patients reported that they could see better to sew, thread needles, and read, we would think that the medication had unusual merit, even if the improvement was caused by the placebo. We all know how this disease goes relentlessly onward, and any improvement is of great importance when nothing else can be offered. If symptomatic improvement occurs, it does not always follow that objective improvement is necessarily concomitant. The objective improvement that does accompany symptomatic relief may be functional, and

not visible on examination. Is the disturbance of vision entirely caused by the hemorrhages, aneurysms, or exudates, or do these pathologic alterations cause functional retinal changes? Perhaps testosterone corrects the metabolic disturbances of the retina in a manner that we do not yet know.

Structure does not always correspond exactly to function. Similar situations abound in medicine. A patient fully recovered from coronary thrombosis may continue to show abnormalities in his electrocardiogram for months or years after clinical recovery. A patient with a severe psychosis may show no pathology in the lesion at autopsy. Did not the psychosis exist?

A patient with cirrhosis of the liver may show very severe pathology in a liver biopsy specimen and yet may feel quite well. Another patient, with mild histological changes, may be moribund. Liver function tests may more nearly determine the true state of affairs. After all, the patient comes because of a derangement of function, and if the hormones can improve his visual function, they are worth-while drugs, even if one does not yet know how they work.

Now as to Dr. Bedrossian's own tables. There are at least seven patients who were improved with hormonal therapy. With saline, the large majority were worse or remained the same, but showed no improvement. Only one patient was slightly better with saline. This remission, conceivably, could have been spontaneous. Does that mean that the placebo treatment was as effective as the hormonal treatment? We do not profess to know very much about statistics, but it reminds us of the old saw, "Statistics can prove anything." In addition, we feel that Dr. Bedrossian so classifies his cases that moderate amounts of improvement would be lost. This moderate amount of improvement is important in a disease in which progression is as relentless as in diabetic retinopathy.

Recently several articles have appeared reporting salutary effects from our method of treatment.

Hensius (*Therapiewoche* **6: 7** [Feb.] 1952) used testosterone, 15 mg. three times a week, and found 40% of his patients with diabetic retinopathy definitely improved, 15% slightly improved, 25% unchanged, and 20% worsened. In his report to the 57th Conference of the German Ophthalmological Society in Heidelberg, 1951, he reported the same findings. Bertram (*Therap. Gegenw.* **90:** 321 [Sept.] 1951) gives the possible rationale of the testosterone treatment, which he believes counteracts adrenal hyperactivity in diabetes retinopathy. In addition, we have personal communications from both Dr. Hensius and Dr. Bertram attesting to the continued effectiveness of the hormonal method of treatment. We have also a personal communication from Dr. Henry Dolger, of the Mount Sinai Hospital, New York, who claims 40% effective results with our therapy in diabetic retinopathy.

Our own final report, covering about three years of work on a larger series of patients, is now being collated; and, while we have no definite figures at this time, the results still appear to be far better than those with any previous form of therapy known to us.

Since our original paper, additional evidence has been reported which supports our form of therapy.

Becker (*Ann. Int. Med.* **37:** 273, 1952), reporting the work of Friedenwald and Becker, was successful in reproducing lesions similar to diabetic retinopathy in humans by injecting rabbits with alloxan and corticotropin. At autopsy the retinas of these rabbits showed definite aneurysms. Lawrence (*Brit. J. Ophth.* **32:** 461, 1948) reported two cases in which diabetic retinopathy developed during pregnancy and cleared after delivery. These observations suggested that the increased endogenous corticotropin during pregnancy might play a role in diabetic retinopathy. Becker (*Ann. Int. Med.* **37:** 273, 1952) noted lesions resembling capillary aneurysms in the fundi of two patients following corticotropin treatment for sarcoid. These lesions regressed after cessation of treatment.

Poulsen (*Diabetes* **2:7**, 1953) describes the case of a woman who developed diabetes at the age of 9 years and showed diabetic retinopathy with scattered hemorrhages when she became pregnant, at the age of 30. After delivery she developed typical Simmonds' disease, a pituitary lesion with loss of sexual function, loss of axillary and pubic hair, subnormal basal metabolism, low blood pressure, and amelioration of the diabetes. Within four years the diabetic retinopathy was diminished, and within six years no signs were present.

These observations suggest that increased endogenous corticotropin in the diabetic patient may be the cause of diabetic retinopathy. How can we antagonize the hormone? So far, testosterone and the estrogens are the only effective antagonists to many of the actions of corticotropin. True, all of the actions are not antagonized.

Another, less practical method of treatment based on the same theoretical considerations has been the "possible cure" of diabetic retinopathy by bilateral adrenalectomy, as reported by Green (*J. A. M. A.* **144:** 439, 1950).

Testosterone and the estrogens are not the final answer to diabetic retinopathy, but it would be grave injustice to close the door forever on a promising clue.

LOUIS PELNER, M.D.
SAMUEL WALDMAN, M.D.
1352 Carroll St., Brooklyn 13.

News and Comment

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Second National Conference on Trichinosis.—The Second National Conference on Trichinosis will be held in the auditorium of the American Medical Association, 535 N. Dearborn St., Chicago, on Monday, March 1, 1954. The purposes of this conference are to discuss methods of education, problems of human and animal health, and research in relation to control of this disease. For further information, write to Dr. S. E. Gould, chairman, Wayne County General Hospital, Eloise, Mich.

Postgraduate Course in Basic Ophthalmology, Wayne University.—The tuition fee for the postgraduate training course in basic ophthalmology to be given at Wayne University Graduate School of Medicine has been reduced to $500.

American Orthoptic Council.—The basic course in orthoptics for technicians sponsored by the American Orthoptic Council will be held in 1954 in the Department of Ophthalmology, University Hospitals, Iowa City.

The course will consist of didactic lectures and practical demonstrations, given by outstanding teachers. It will be held from June 17, 1954, through July 3, 1954.

Requests for further information about the course or application for admission should be addressed to Hermann M. Burian, M.D., chairman, committee on instruction, University Hospitals, Iowa City.

SOCIETY NEWS

Chicago Ophthalmological Society.—The annual clinical conference of the Chicago Ophthalmological Society will be held on Friday and Saturday, Feb. 5 and 6, 1954, at the Drake Hotel. The tenth annual Gifford Memorial Lecture will be presented by Dr. Kenneth Swan, Portland, Ore., on "The Blind Spot Mechanism."

The Ophthalmological Society of Egypt.—The Society will hold its annual meeting at the Memorial Ophthalmic Laboratory, Giza, Egypt, at 9 a.m. on Friday and Saturday, March 12 and 13, 1954. Medical practitioners, oculists or others, are cordially invited.

Dr. Sabri Kamel, Dar El Hekmah, 42 Kasr El Ainy St., Cairo, Egypt, is secretary of the Society.

Books

May's Manual of Diseases of the Eye. Edition 21. Edited by Charles A. Perera, M.D. Price, $6. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

This excellent compendium of ophthalmology has now gone through 21 editions since Dr. Charles May published the first edition, in 1900. It has been carefully brought up to date and will undoubtedly continue to serve a useful purpose for those who wish a very condensed view of the whole of ophthalmology.

The chief objection to such books for teaching medical students is their attempt to give a little about everything, so that, in order that texts may be kept small, some important subjects must suffer.

Advances in Ophthalmology. Edited by E. B. Strife, Lausanne. Price, 39.50 Swiss francs. S. Karger, Holbeinstrasse 22, Basle, and 215 Fourth Ave., New York, 1953.

This second edition contains papers entitled "The Structure of the Vitreous Body," by A. Grignolo; "Electrophysiology of the Eye of Man," by M. Monnier; "Normal and Pathological Anatomy of the Eye," by F. Rintelen; "The Orbit and Ocular Adnexa and the Skull," by E. Godtfredsen; "Injuries of the Eyes," "Industrial Ophthalmology," and "Insurance and Social Medicine and Matters of the Blind," by R. J. Hesberg, and "Trachoma," by G. B. Bietti. Only the articles by Godtfredsen and Hesberg are in English; the others are either in French or in German.

The main objection to this type of book is the approach, which seems to be the inclusion of as many articles as have occurred in the current literature, without regard to the relative value. The chief value is the excellent collection of references, and for this purpose the book is recommended.

Handbook for the Blind. By Juliet Bindt. Price, $3.50. Pp. 244. The Macmillan Company, 60 5th Ave., New York 11, 1952.

This book is intended for the newly blinded and those who work with them. It gives instruction to the blind on their personal appearance and their table manners, advice on deportment in going out alone, and the use of a Seeing Eye dog, and chapters on shopping, homemaking, caring for the baby, and the various activities which may occupy them in earning a living and in their leisure time. There is also an excellent section addressed to the sighted, giving homely advice about their methods of handling blind people.

The volume is an excellent addition to the many books that have recently been published to create better understanding in the care of the blind, in particular by helping the blind adjust to a seeing world. It is a book that can be read by every ophthalmologist with both profit and pleasure.

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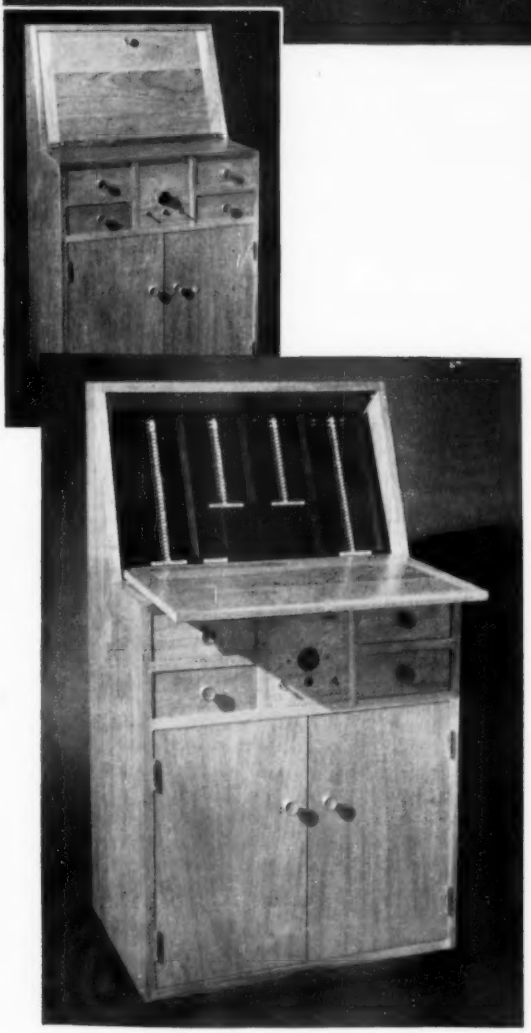

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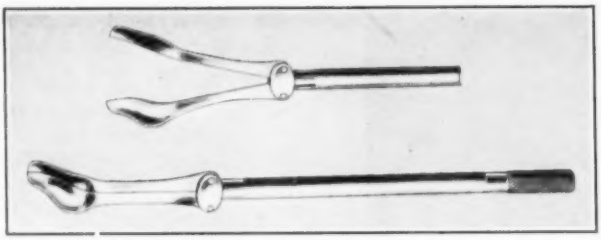

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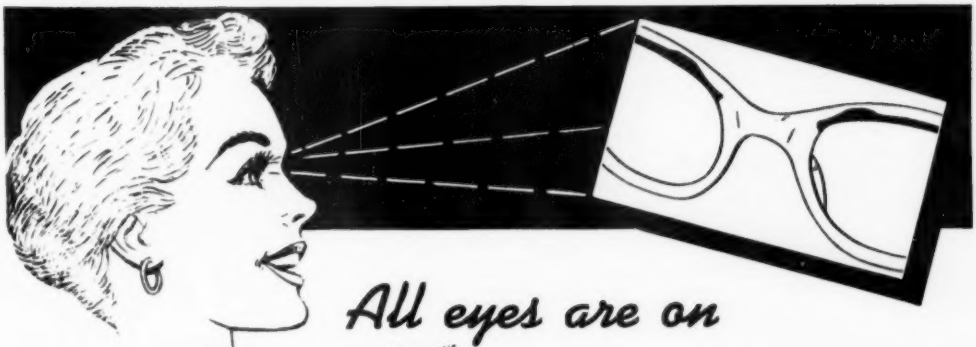

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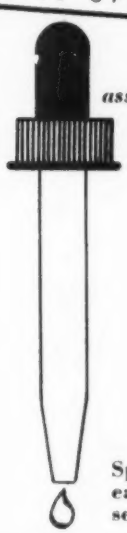

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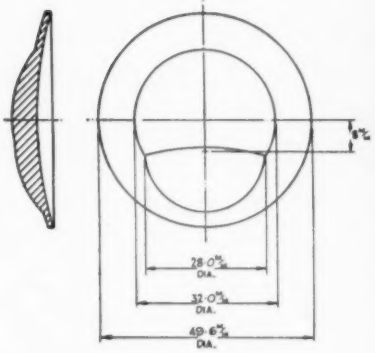

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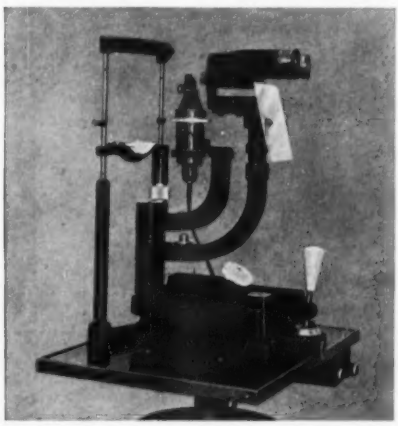

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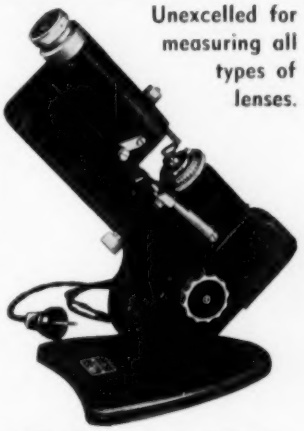

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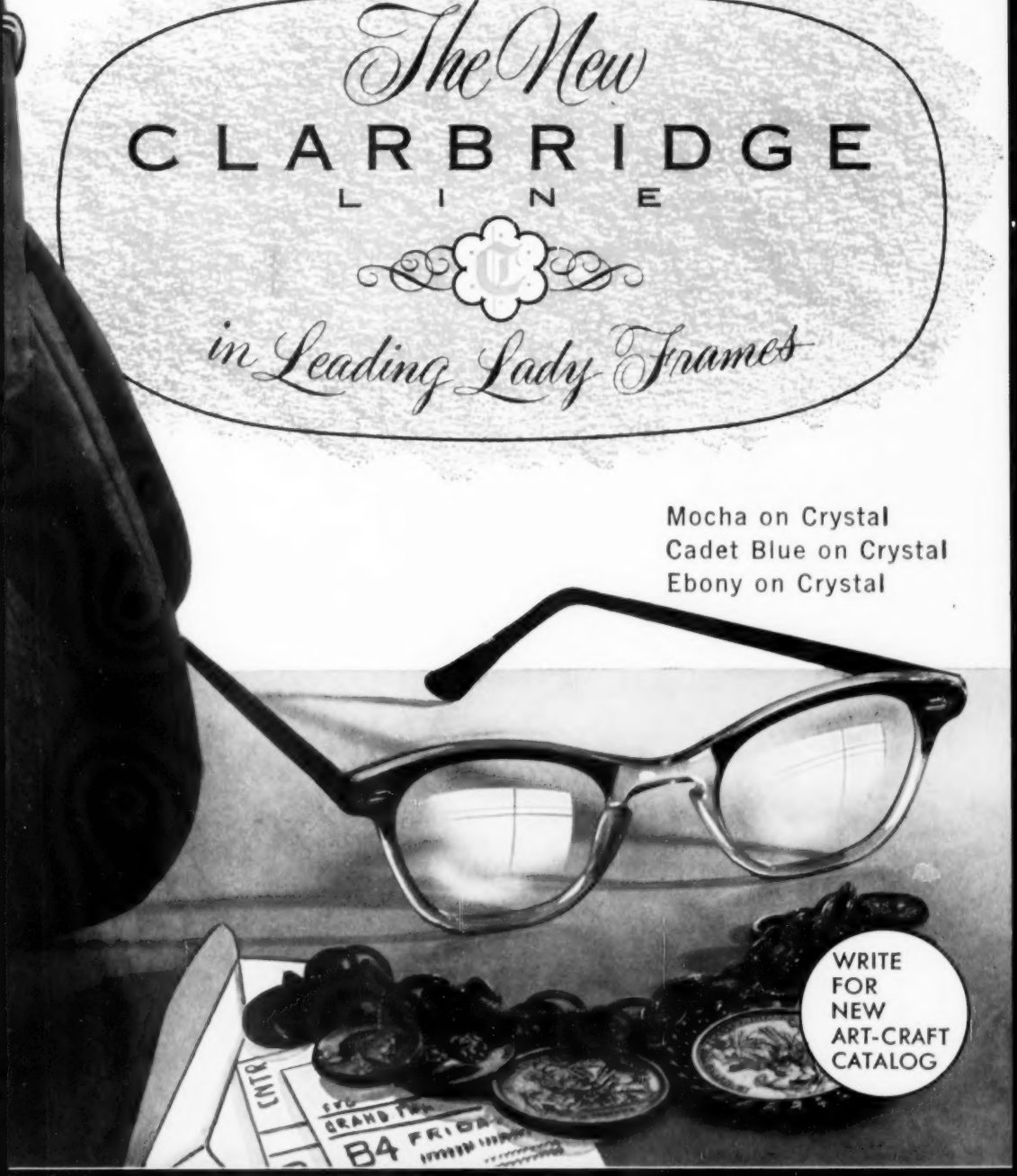

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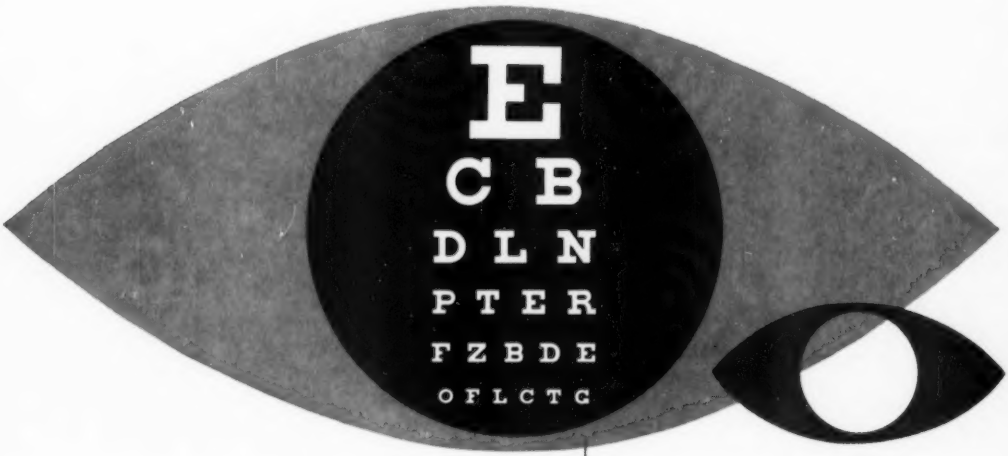

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